CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-320

MEDICAL REVIEW(S)

Addendum to Clinical review of NDA 22-320

In section **2.5 Summary of Presubmission Regulatory Activity Related to Submission**

The additional statement below should be added in the section labeled **Pre-NDA Meeting**

The sponsor clarified that no unblinding of data was performed in Study RD.06.SPR.18094 prior to database lock.

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/s/

Jane Liedtka
12/5/2008 09:03:28 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-320
Submission Code	Original NDA
Letter Date	Feb 8, 2008
Stamp Date	Feb 8, 2008
PDUFA Goal Date	Dec 8, 2008
Reviewer Name	Jane Liedtka, M.D.
Review Completion Date	Oct 22, 2008
Established Name	Adapalene0.1%/Benzoyl Peroxide Gel 2.5%
(Proposed) Trade Name	Epiduo
Therapeutic Class	retinoid/oxidizing agent
Applicant	Galderma Laboratories LP
Priority Designation	S
Formulation	Gel
Dosing Regimen	once per day
Indication	Acne Vulgaris
Intended Population	ages 12 and older

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

The applicant has submitted a marketing application for a new fixed combination product containing the two active ingredients adapalene 0.1% and benzoyl peroxide 2.5% for the proposed indication of treatment of acne vulgaris in patients aged 12 years and above. Both active ingredients have previously been approved individually for marketing in the United States. The applicant conducted two adequate and well-controlled pivotal trials, and the studies were of appropriate design to demonstrate the contribution of each component to efficacy so as to comply with the combination policy, as put forth in 21 CFR 300.50. Specifically, the combination product was compared to each monad in the product vehicle (the product was also compared to vehicle itself). This reviewer considers the applicant to have submitted adequate evidence of effectiveness of the combination product for treatment of acne vulgaris.

A total of 1401 subjects have been exposed to adapalene/BPO gel in this development program. The designs of the pivotal studies were generally adequate to assess the safety of the product for its intended use. Topical safety was adequately evaluated in the development program and included assessment for local adverse events and formal dermal safety studies.

This reviewer recommends that EPIDUO be approved for the topical treatment of acne vulgaris in patients 12 years and older.

1.2 Risk Benefit Assessment

This reviewer concludes that Adapalene/Benzoyl Peroxide Gel has a favorable benefit/risk profile for the treatment of acne vulgaris in patients 12 years and older. Adapalene/Benzoyl Peroxide Gel is superior to the individual monads and Gel Vehicle with an acceptable safety profile. The two active ingredients (adapalene 0.1% and benzoyl peroxide 2.5%) have been in clinical use for more than 10 years for adapalene and for more than 20 years for benzoyl peroxide with no significant safety signals noted. The combination product allows once daily use facilitating compliance and preserving efficacy.

1.3 Recommendations for Postmarketing Risk Management Activities

The standard risk management measures of prescription status, professional labeling and spontaneous adverse event reporting are adequate to address the post marketing safety for this

drug product. No new significant safety concerns were evident in the phase 3 studies performed with adapalene/benzoyl peroxide gel as compared to previously approved formulations of topical adapalene 0.1% and benzoyl peroxide 2.5%.

1.4 Recommendations for other Post Marketing Study Commitments

There are currently no clinical Phase 4 commitments.

2 Introduction and Regulatory Background

2.1 Product Information

The proposed drug product, Adapalene 0.1%/Benzoyl Peroxide 2.5 % Gel, is a new fixed-dose combination of adapalene 0.1% (w/w) and benzoyl peroxide 2.5% (w/w) intended for the treatment of acne vulgaris in patients 12 and older. It is a white to very pale yellow opaque gel, containing 0.1% w/w (1 mg/g) of adapalene and 2.5% w/w (25 mg/g) of benzoyl peroxide, as the drug substances, dispersed in an aqueous gel dosage form, for the topical treatment of acne vulgaris. It is packaged in plastic tubes ——— with a ⌜ ⌟ head and ⌜ ⌟ screw closure cap from two suppliers ⌜ ⌟ Tube sizes proposed for marketing are — 45 g, ⌜ ⌟ b(4)

———

Adapalene is a naphthoic acid derivate and retinoid analogue with actions similar to those of retinoids. Benzoyl peroxide is commonly used as antimicrobial and keratolytic agent in the commercial production of topical drug products, with more than 20 different prescription or over-the-counter drug products currently marketed worldwide.

See section 4.1 (CMC) for list of the inactive ingredients.

2.2 Currently Available Treatments for Proposed Indications

There are a number of products approved for treatment of acne vulgaris. These treatments include both topical and systemic products. Pharmacologic categories of approved therapies for acne vulgaris include topical antibiotics (e.g. erythromycin, clindamycin), topical retinoids (e.g. tretinoin, tazarotene) and systemic hormonal therapies (e.g. ethinyl estradiol/norgestimate).

2.3 Availability of Proposed Active Ingredient in the United States

Adapalene is widely used in the commercial production of prescription topical drug products. Three different formulations are currently marketed in the USA: Differin® gel 0.1% (NDA# 020380), Differin® cream 0.1% (NDA# 020748) and Differin® gel 0.3% (NDA# 021753).

Benzoyl peroxide is widely available, with more than 20 different prescription or over the counter drug products currently marketed worldwide (e.g. Cutacnyl® [benzoyl peroxide] 2.5% gel, Benzac® AC [benzoyl peroxide] gel, marketed by Galderma in US).

2.4 Important Safety Issues with Consideration to Related Drugs

Adapalene, though structurally distinct from retinoic acid is considered a "retinoid" since it acts at retinoic acid receptors. Retinoids are irritants and known teratogens. Use of these products may also make for heightened sun sensitivity because topical retinoids may decrease the number of layers in the stratum corneum.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The development program was conducted under IND 67,801.

PreIND meeting: July 28, 2003

- Advice from the biopharmaceutics/clinical pharmacology reviewer included:

  > The sponsor is requested to conduct a classical PK study with a duration of at least 30 days of daily applications with appropriate blood sampling at steady-state (3-week) and at the end of dosing (4-week) intervals.

- Advice from the clinical reviewer included :

  > The Sponsor has conducted irritation, sensitization, phototoxicity and photosensitization studies in healthy adults in Europe. These studies may need to be repeated with the final to be marketed formulation if a different formulation was used then the one intended for final use.
  >
  > It is recommended that pregnancy tests be conducted on females of child-bearing potential at monthly intervals through the course of the 12 week study, while effective contraception is to be encouraged while using the drug product.

The sponsor was asked to submit data on any pregnancies and their outcome to the agency for evaluation.

The primary efficacy endpoints should be

a. The success rate based on the Investigator Global Scale (the percentage of patients graded as clear or almost clear) as a static assessment at the efficacy endpoint and not a change from baseline.
b. Percent reduction from baseline of facial non-inflammatory and inflammatory lesions.

The secondary efficacy endpoints should be

a. The Response rate (the percentage of subjects that reached 50% reduction in lesion counts).
b. Patient's assessment of the acne (graded 0-5, 0 being clear and 5 being worse).

It is recommended that the sponsor include lab evaluations (cbc, Comprehensive Metabolic profile and U.A.) as part of the protocol for the Phase 2 study. The Agency agreed that if the planned PK and lab studies did not show significant absorption or systemic side effects, lab monitoring may not be needed as part of further studies.

End of Phase 2 Meeting: Dec 12, 2005

- Advice from the Biostatistics reviewer included:

Whether the completed study RD.06.SPR.18094 can be used to establish the efficacy claim for Adapalene/BenzoylPeroxide topical gel is a review issue which will depend on the study design, statistical method of analysis, and the efficacy findings. In general, the agency requires efficacy established based on two well designed independent Phase3 trials.

The Division stated that study (RD.06.SPR.18094) was a phase 2 trial and the study synopsis stated that "Study unblinded as prospectively defined in the protocol". It is not clear when the unblinding was done. In addition, the study was powered at 80% to detect a 15% difference in success rate and percentage change in lesion counts.

It should be noted that the sponsor might be taking a risk by planning to conduct only one additional phase 3 trial (18087) to support their efficacy claim.

- Advice from the clinical reviewer included:

  The Division recommends co-primary endpoints that evaluate an IGA and acne lesion counts to evaluate efficacy in acne trials. Also the division recommends an IGA with five severity grades; clear (0), almost clear (1), mild severity (2), moderate severity (3), and severe (4).

Pre-NDA Meeting: Dec 14, 2007

- Advice from the clinical reviewer included

  Please clarify whether Study RD.06.SPR.18094 which was discussed at the EOP 2 meeting as a phase 2 study with concerns regarding adequacy due to blinding among other issues is the same study as RD .06.SPR.18094, which you propose to be submitted as one of the two adequate and well-controlled trials in this submission.

  The adequacy of the dermal safety evaluation will also be a review issue. The numbers of subjects in the phototoxicity study (25 instead of 30), photosensitization study (33 instead of 45), and cumulative irritation study (25 instead of 35) are less than those typically recommended by the division.

2.6 Other Relevant Background Information

Pediatric Waiver Request

The Applicant has requested a waiver of the requirement to assess the use of the drug in pediatric patients less than 12 year of age. As their reason for this waiver request they state:

> Since acne vulgaris usually develops after the onset of puberty and largely affects teenagers and young adults, the Applicant certifies that adequate and well-controlled studies to evaluate the drug in patients less than 12 years of age would be highly impractical.

The applicant has not submitted any references or data to substantiate this statement. According to the Guidance "How to Comply with the Pediatric Research Equity Act" the applicant must provide evidence of a lack of adequate numbers of patients with acne in the age group under 12 years. Until they provide such evidence the most they would qualify for at this point is a deferral.

In Fitzpatrick's "Dermatology in General Medicine" in chapter 78 entitled "Acne Vulgaris and Acneiform Eruptions" it states:

> In girls, the occurrence of acne may precede menarche by more than one year.....The age of onset of acne varies considerably. It may start as early as 6 to 8 years of age or it may not appear until the age of 20 years or later.

In the article "Age at Menarche and Racial Comparisons in US Girls" by Chumlea *et al.* published in *Pediatrics (2003)*111, 110-113 the author states

> "From NHANES III data collected between 1988 and 1994....that mean age of menarche was 12.43 years"

By extrapolation this would put the **mean** age of acne onset at 11.43 years with 50% of patients having onset at an earlier time. This reviewer recommends deferral of studies in subjects under 12 years and waiver of subjects below the age of 8 years.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No study site investigations by the Division of Scientific Integrity were performed. The applicant's analyses were reviewed, and independent analyses were performed by the Agency biostatistics reviewer.

3.2 Compliance with Good Clinical Practices

The applicant affirmed that the studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Conference on Harmonization (ICH) guideline E6: Good Clinical Practice (GCP). All subjects were informed about the study and provided the opportunity to ask questions. Subjects, or their legal representatives, read, signed, and dated the IRB-approved consent form before taking part in any study activity. For subjects under the age of 18, an IRB-approved assent also was obtained.

3.3 Financial Disclosures

The applicant certified in Form 3454 that they had not entered into any financial arrangements with any of the clinical investigators.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

4.2 Adapalene/Benzoyl Peroxide Gel is a white to very pale yellow opaque gel, containing 0.1% w/w (1 mg/g) of adapalene and 2.5% w/w (25 mg/g) of benzoyl peroxide, as the drug substances, dispersed in an aqueous gel dosage form, for the topical treatment of acne vulgaris.

Table 1 provides a list of all components, their percentage (w/w) in Adapalene/Benzoyl Peroxide Gel, and their quality standards.

Table 1 **Adapalene/Benzoyl Peroxide Gel: Qualitative and Quantitative Composition**

Components	Function	Percent Formula (w/w)	Quantity per 1 g	Reference to Quality standards
Active Components				
Adapalene	Active Ingredient	0.10	0.001	In-house specifications
Benzoyl Peroxide	Active Ingredient; antimicrobial	2.50	0.025	In-house specifications [2]
Excipients				
Simulgel 600 PHA[3]	Gelling agent			In-house specifications
Docusate Sodium				USP
Edetate Disodium				USP
Glycerin				USP
Poloxamer 124				USP
Propylene Glycol				USP
Purified Water				USP

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[1] This overage was discussed in IND 067,601 SN: 019 and accepted by FDA CMC reviewer (memo dated February 3, 2004)
[2] The in-house monograph corresponds to USP monograph with addition of specifications for particle size and modification of HPLC method for impurities
[3] Simulgel 600 PHA (copolymer of acrylamide and sodium acryloyldimethyltaurate, isohexadecane, polysorbate 80, sorbitan oleate) is a non-compendial component. Refer to Sections 3.2.P.4.6 and 3.2.A.3 for detailed information

Source: Sponsor's Section 3.2.P.1 Description and Composition of The Drug Product

The CMC review has not been finalized as of the date of this review.

4.3 Clinical Microbiology

Consultation with Clinical Microbiology is pending at the time of this review. There are no microbiology studies in the submission. The consultation is for labeling regarding the proposed language for the mechanism of action of benzoyl peroxide in the package insert.

4.4 Preclinical Pharmacology/Toxicology

The conclusion of the pharmacology/toxicology reviewer, as stated below in his review, is that EPIDUO is approvable from a pharmacological/toxicological perspective:

> A comfortable safety profile for the fixed–combination EPIDUO (adapalene 0.1% and benzoyl peroxide 2.5%) Gel has emerged from the merger of individual safety profiles of adapalene and BZPO, and a few bridging studies conducted with the combination gel. Adapalene in 0.3% gel formulation did not cause any systemic toxicity; and 1-10% BZPO as a single moiety or in combination with other consumer chemicals including drugs was found to be safe. In addition, the evaluation of combination gel undoubtedly established that the two active ingredients acted independently without potentiating, synergizing, or antagonizing the local or systemic effect(s) of each other.

The pharmacology/toxicology reviewer also noted:

> It is important to note that adapalene like other retinoids can induce teratogenicity at sufficiently high systemic doses (oral doses from 25mg/kg/day). A dermal NOAEL of 36 and 72mg/m2/day was established in rat and rabbit embryo-toxicity studies, respectively. This dose is 29-59 times greater than the maximum recommended dose.

4.5 Clinical Pharmacology

4.5.1 Mechanism of Action

EPIDUO Gel combines two active substances, adapalene 0.1% and benzoyl peroxide 2.5%, which act through different mechanisms of action in acne vulgaris.

According to the label for Differin 0.3%, adapalene acts on retinoid receptors. Biochemical and pharmacological profile studies have demonstrated that adapalene is a modulator of cellular differentiation, keratinization, and inflammatory processes all of which represent important features in the pathology of acne vulgaris. Mechanistically, adapalene binds to specific retinoic acid nuclear receptors but does not bind to the cytosolic receptor protein. Although the exact mode of action of adapalene is unknown, it is suggested that topical adapalene normalizes the differentiation of follicular epithelial cells resulting in decreased microcomedone formation.

According to the sponsor, benzoyl peroxide is an oxidizing agent with broad spectrum bactericidal activity, in particular against Propionibacterium acnes (P. acnes), demonstrated in vitro and in vivo. Its effect in acne vulgaris is probably related to a decrease in the bacterial population of P. acnes with an accompanying decrease in the production of irritating fatty acids in sebum.

4.5.2 Pharmacodynamics

According to the sponsor, early onset of action with a decrease of inflammatory lesions (papules and pustules) is seen as early as one week after treatment initiation. Noninflammatory lesions (open and closed comedones) respond between the first and fourth week of treatment. The overall response is sustained with continuing treatment at three months.

Time course evaluation of local tolerability symptoms of erythema, scaling and stinging/burning were highest at week one and subsided thereafter with EPIDUO Gel. The incidence of signs and symptoms of irritation was comparable between EPIDUO Gel and adapalene gel 0.1%, and slightly higher compared to benzoyl peroxide gel, 2.5% and gel vehicle.

4.5.3 Pharmacokinetics

According to the sponsor, in a 30-day clinical PK study conducted in 24 patients with acne who were treated with either the fixed-combination gel or with an adapalene 0.1% matched formula under maximized conditions (with application of 2 g gel/day), adapalene was not quantifiable in the majority of plasma samples (limit of quantification 0.1 ng/mL). Low levels of adapalene (Cmax between 0.1 and 0.2 ng/mL) were measured in two subjects treated with EPIDUO Gel and in three subjects treated with Adapalene 0.1% Gel. The highest adapalene AUC 0-24h determined in the fixed combination group was 1.99 ng.h/ml.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

The following table from the sponsor's Clinical Overview (page 13) lists the studies completed at the time of this NDA's submission. All of these studies were reviewed.

Table 2 Summary of Completed Clinical Studies

Study No.	Population (subjects)	Study Type	Number of Subjects on Adapalene/Benzoyl Peroxide Gel*	Total number of Subjects in Study
Clinical Pharmacology Studies - Healthy Subjects				
SRE.2674	Healthy	L/R Comparison (Split Face) Study with two Products each to Optimize Dose	31	60
SRE.2687 + Amendment 01	Healthy	Comparative Cumulative Irritation Potential Study	25	25
SRE.2683 + Amendment 01 + Amendment 02	Healthy	Cutaneous Sensitization Potential Study	251	251
SRE.2681 + Amendment 01 + Amendment 02	Healthy	Phototoxic Potential Study	25	25
SRE.2682 + Amendment 01	Healthy	Photoallergy Potential Study	33	33
Total Exposure in Healthy Subjects			365	394
Pharmacokinetics Studies - Subjects with *acne vulgaris*				
SRE.2685	Acne vulgaris	Ten-Day PK Study	8	16
SRE.18097	Acne vulgaris	Thirty-Day PK Study	12	24
Total Exposure in pharmacokinetics studies			20	40
Efficacy and Safety Studies - Subjects with *acne vulgaris*				
SRE.18094	Acne vulgaris	Efficacy and Safety Study (12-week treatment)	149	517
SRE.18087	Acne vulgaris	Efficacy and Safety Study (12-week treatment)	415	1668
SRE.18089	Acne vulgaris	Long-Term Safety and Efficacy Study (12-month treatment)	452	452
Total Exposure in efficacy and safety studies			1016	2637
Total Exposure in Subjects with *acne vulgaris*			1036	3037
Total Subjects Exposed to Formulations			1401	3071

* All studies in this table were conducted with the to-be-marketed formulation except SRE.2674.

5.2 Review Strategy

Study 18087, the single phase 3 trial submitted, was reviewed in depth. Study 18094, the phase 2 trial that the sponsor has submitted as their second pivotal trial, was also reviewed in depth. Details about these studies are outlined in section 5.3.

The safety data collected in the two well-controlled 12 week studies (18094 and 18087) are integrated for the safety analysis.

The following studies were also reviewed in depth with regard to the safety analysis:

- Four dermal safety studies in healthy subjects; SRE.2687, SRE.2683, SRE.2681, and SRE.2682
- One dose finding study in healthy subjects (SRE.2674)
- Two pharmacokinetic studies in subjects with acne vulgaris (SRE.2685 and SRE.18097).
- One open-label, long-term safety and efficacy study (SRE.18089).

5.3 Discussion of Individual Studies

Clinical Study: Protocol Number SRE. 18094

Title: A Multicenter, Randomized, Double-Blind, Parallel Group Study to Evaluate the Safety and Efficacy of a Fixed Combination of Adapalene 0.1% and Benzoyl Peroxide 2.5% (Adapalene and Benzoyl Peroxide Topical Gel) Gel Compared to Each Monad and Topical Gel Vehicle in Subjects with Acne Vulgaris

Objective: To evaluate the efficacy and safety profile of Adapalene and Benzoyl Peroxide Topical Gel versus Adapalene 0.1% Topical Gel, Benzoyl Peroxide 2.5% Topical Gel and Topical Gel vehicle in the treatment of acne vulgaris for up to 12 weeks.

Drug Development Phase:

Study 18094 was a Phase 2 trial originally discussed at the Pre-IND meeting held on 8/14/03. The study was conducted from Feb 17, 2004 to Dec 21, 2004. At the EOP2 meeting held on Dec 12, 2005 this study was presented as one of the pivotal trials and the Agency responded with the following statement:

> Whether the completed study RD.06.SPR.18094 can be used to establish the efficacy claim for Adapalene/Benzoyl Peroxide Topical Gel is a review issue which will depend on the study design, statistical method of analysis, and the efficacy findings. In general, the agency requires efficacy established based on two well designed independent Phase 3 trials….. In addition, the study was powered at 80% to detect a 15% difference in success rate and percent change in lesion counts.

Study Design: A multicenter, randomized, double-blind, parallel- group, active comparator and vehicle controlled study

Number of Subjects: 490 subjects, 140 per active treatment group and 70 in the vehicle group

Ages of Subjects for Inclusion: Male and female subjects 12 years of age or older

Inclusion Criteria:

1. Male and female subjects 12 years of age or older.
2. A clinical diagnosis of acne vulgaris with facial involvement.
3. A minimum of 20 but not more than 50 inflammatory (papules and pustules) lesions on the face (excluding the nose).
4. A minimum of 30 but not more than 100 non-inflammatory lesions (open comedones and closed comedones) on the face (excluding the nose).
5. All Females of non-childbearing potential or with a negative urine pregnancy test at the beginning of the study. Non-childbearing potential is defined as: premenstrual, post menopausal (absence of menstrual bleeding for 1 year prior to enrollment), hysterectomy or bilateral oophorectomy.
6. Female subjects of childbearing potential practicing an approved method of contraception and willing to continue to use for the duration of the study: oral contraception (must have been on a stable dose for 6 months prior to study entry), bilateral tubal ligation, IUD, systemic (injectable) contraception, double barrier, strict abstinence.
7. Willingness and capacity for protocol compliance (for subjects under 18 years of age, the parent/guardian must be wiling and able to comply with study requirements).
8. Consent to participate, verified by signing an approved written Informed Consent Form, or for subjects under age 18, an assent form in conjunction with a signed Informed Consent Form from the parent/guardian.
9. Apprised of the Health Insurance Portability and Accountability Act (HIPAA). Willing to share personal information and data as verified by signing a written authorization, as applicable.

Exclusion Criteria:

1) Nodules or cysts.
2) Pregnancy, nursing, or planning a pregnancy.
3) Clinically significant abnormal findings or condition (other than acne), which might, in the opinion of the Investigator, interfere with study evaluations or pose a risk to patient safety during the study.
4) Acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne, etc.), or severe acne requiring systemic treatment.
5) Underlying diseases or other dermatological conditions that require the use of interfering topical or systemic therapy such as, but not limited to, atopic dermatitis, perioral dermatitis or rosacea.
6) Use of prohibited medications prior to or during the study.

Specified washout period(s) to Baseline for topical preparations on the face:

- Alpha hydroxy acid products, medicated shaving creams, astringents, preparations with alcohol- 1 day
- Phototherapy devices for acne (e.g., clearLight™), adhesive cleansing strips (e.g., Ponds, Biore)- 1 week

- corticosteroids, antibiotics, retinoids- 4 weeks
- Other anti-inflammatory drugs, other topical acne treatments- 4 weeks

Specified washout period(s) to Baseline for systemic medications:

- corticosteroids, anti-inflammatories, antibiotics- 4 weeks
- Other oral acne treatments (including Isotretinoin)- 6 months
- Note: Oral vitamin A up to the recommended daily dose, 4,000-5,000 IU is acceptable
- Note: Aspirin for prophylactic use, up to 325mg, is not considered to be an anti-inflammatory dose.
- Note: Only plain penicillin is allowed.

7) Known sensitivities to the study preparations (see Investigator's Brochure).
8) Beard or facial hair which might interfere with study assessments.
9) Participation in another investigational drug or device research study within 30 days of enrollment.
10) Refusal of photographic procedures.

Study Plan:

This is a multicenter, randomized, double blind, parallel-group active and vehicle controlled study involving subjects with acne vulgaris. Patients will be randomized in a 2:2:2:1 ratio to Adapalene and Benzoyl Peroxide Topical Gel, Adapalene 0.1% Topical Gel, Benzoyl Peroxide 2.5% Topical Gel, or Topical Gel Vehicle. After a screening visit, qualified subjects will be randomized at the Baseline visit and treated for a period of up to 12 weeks. Subjects will return to centers for evaluations at Weeks 1, 2, 4, 8 and 12. A urine pregnancy test is required at both the Baseline and final visits for all females of childbearing potential.

Data Analysis:

Several comments were provided in the review of the protocol for Study 18094 which were not incorporated into the statistical analysis section of the protocol. In the review of the protocol for Study 18087 the Division and sponsor reached agreements on the statistical analysis of the primary endpoints. As the statistical analysis details are more well-defined and the endpoints are in agreement with the Division, these agreed upon statistical methodologies are applied to both the studies submitted to the NDA. Thus, the statistical methodologies described below correspond to those included in the protocol for Study 18087 and not those included in the protocol for Study 18094.

All comparisons of EPIDUO to its monads and vehicle for the co-primary endpoints will be tested at the two-sided @ = 0:05 significance level. Small centers will be pooled prior to analysis which combines the largest center with the smallest center. These pooled centers will be referred

to as "analysis centers" in the statistical analyses. The trial will meet efficacy criteria if all primary analyses are shown to be statistically significant at the two-sided @= 0:05 level.

Study Sites:

Investigator #	Name	Address	Number of subjects
2123	[redacted]	[redacted]	1
2184			20
2185			6
2238			19
2028			39
2102			29
2243			7
2240			10
2205			10
2114			3
2084			39
2220			4
2551			21
2050			9
2157			13
2189			12
2020			32
2015			20
2027			12
2069			10
2095			28
2208			28
2087			9
2094			15
740			13
2001			3
2132			11
385			6
2248			2
2169			7
2065			10
2153			5
429			28
2051			5
1086			10
438			21

b(4)

Discussion of study populations, patient disposition, demographics, discussion and conclusions will be combined for studies 18094 and 18087 after basic protocol review of 18087.

Clinical Study: Protocol Number SRE.18087

Title: A Multicenter, Randomized, Double-Blind, Parallel-Group Study to Demonstrate the Efficacy and Safety of Adapalene/Benzoyl Peroxide Topical Gel Compared with Adapalene Topical Gel, 0.1%; Benzoyl Peroxide Topical Gel, 2.5% and Topical Gel Vehicle in Subjects with Acne Vulgaris

Objective:

The primary objective is to demonstrate the superiority in efficacy and assess safety of Adapalene/Benzoyl Peroxide Topical Gel (Adapalene/Benzoyl Peroxide Gel) versus Adapalene Topical Gel, 0.1% (Adapalene Monad); Benzoyl Peroxide Topical Gel, 2.5% (Benzoyl Peroxide Monad) and Topical Gel Vehicle (Gel Vehicle) in the treatment of acne vulgaris for up to 12 weeks.

Drug Development Phase: 3

Study Design: multi-center, randomized, double-blind, parallel group, active comparator and vehicle controlled study

Number of Subjects: 1668 subjects were enrolled

Ages of Subjects for Inclusion: 12 years of age or older

Inclusion Criteria:

1. Male and female subjects 12 years of age or older.
2. A clinical diagnosis of acne vulgaris with facial involvement.
3. A minimum of 20 but not more than 50 inflammatory lesions (papules and pustules) on the face (excluding the nose) and not more than one acne nodule.
4. A minimum of 30 but not more than 100 noninflammatory lesions (open comedones and closed comedones) on the face (excluding the nose).
5. A score of "3" (Moderate) on the IGA scale.
6. Females of childbearing potential (including premenstrual subjects) with a negative urinary pregnancy test or females of non-childbearing potential, defined as postmenopausal (absence of menstrual bleeding for 1 year prior to enrollment), hysterectomy or bilateral oophorectomy.
7. Willingness and ability to comply with the protocol (for subjects under 18 years of age or Age of Majority, the parent/legal representative must also have been willing and able to comply with study requirements).

8. Consent to participate, verified by signing an approved written Informed Consent Form, or for subjects under age 18 or Age of Majority, an assent form signed by the subject in conjunction with an Informed Consent Form signed by the parent/legal representative.
9. For U.S. subjects only, apprised of the HIPAA. Willingness to share personal information and data as applicable as verified by signing a written authorization.

Exclusion Criteria:

1. More than one acne nodule.
2. Any acne cyst.
3. Acne conglobata, acne fulminans, secondary acne (chloracne, drug-induced acne), or severe acne requiring systemic treatment.
4. Known previous participation in an Adapalene/Benzoyl Peroxide Gel investigational study.
5. Underlying diseases that required the use of interfering topical or systemic therapy.
6. Other dermatological conditions that required the use of interfering topical or systemic therapy or that might have interfered with study assessments such as, but not limited to, atopic dermatitis, perioral dermatitis, or rosacea.
7. Beard or facial hair that might have interfered with study assessments.
8. Use of tanning booths or tanning lamps within 1 week prior to Baseline and an unwillingness to refrain from use during the study.
9. Use of hormonal contraceptives, unless subject was on a stable dose, i.e., at least 6 months of treatment prior to the enrollment.
10. Use of hormonal contraceptives solely for control of acne.
11. Use of prohibited medications prior to the study and an unwillingness to refrain from use during the study.

Specified washout period(s) up to Baseline for TOPICAL treatments on the face:

• Phototherapy devices for acne (e.g., ClearLight™) and adhesive cleansing strips (e.g., Pond®, Biore®) as well as cosmetic procedures (i.e., facials, peeling, comedone extraction)	1 week
• Anti-inflammatory drugs, salicylic acid (e.g., Clearasil®, Clean & Clear®)	2 weeks
• Corticosteroids, antibiotics (including antibacterials like benzoyl peroxide containing products, e.g., benzamycin), retinoids, zinc	2 weeks
• Other topical acne treatments (including photodynamic therapy or laser)	2 weeks

Specified washout period(s) up to Baseline for SYSTEMIC medications:

• Anti-inflammatory drugs	2 Weeks
• Corticosteroids	4 Weeks
• Antibiotics (except plain penicillin)	4 Weeks

- Other oral acne treatments (e.g., Isotretinoin, Anti-androgens) 6 Months
- Hormonal contraceptives used for less than 6 months 6 Months

No washout was required for alpha hydroxy acid products, medicated shaving creams, astringents, and preparations with alcohol, but their application was forbidden during study.

Note: Oral vitamin A up to the recommended daily dose of 4000 to 5000 IU was acceptable. Anti-inflammatory medication up to 14 total days was acceptable; however, it was not to be used during the final two weeks of treatment.

12. Known sensitivities to the study preparations.
13. Clinically significant abnormal findings or conditions (other than acne), which might have, in the opinion of the Investigator, interfered with study evaluations or posed a risk to subject safety during the study.
14. Subjects who were pregnant or nursing.
15. Participation in another investigational drug or device research study within 30 days prior to Baseline.

Study Plan:

Study RD.06.SRE.18087 was a multicenter, randomized, double blind, parallel, active- and vehicle-controlled study enrolling subjects with acne vulgaris who met pre-specified inclusion/exclusion criteria. Male and female subjects were to be enrolled who were 12 years of age or older and evaluated with a score of "3" (Moderate) on the Investigator's Global Assessment (IGA).

Approximately 1656 subjects were to be enrolled in the study with 414 subjects in each group. Subjects were to be randomized in a 1:1:1:1 ratio to Adapalene/Benzoyl Peroxide Gel, Adapalene Gel, Benzoyl Peroxide Gel or Gel Vehicle. Subjects who met the inclusion/exclusion criteria and who did not require wash-out were to be randomized at Baseline and treated for a period of up to 12 weeks. Subjects were to return to centers for evaluation at Weeks 1, 2, 4, 8 and 12/Early Termination. A urine pregnancy test was required at both Baseline and Week 12/Early Termination visits for all females of childbearing potential.

Data Analysis: see "data analysis" under study 18094

Study Sites:

Investigator #	Name	Address	Number of subjects
8001			45
8003			51
8009			24
8010			8
8012			26
8013			21
8014			39
8015			23
8016			24
8018			32
8020			30
8021			24
8022			30
8023			18
8024			34
8027			8
8028			43
8029			43
8030			26
8031			39
8032			29
8033			28
8034			45
8035			9
8037			0
8038			36
8039			59
8040			44
8041			13
8042			11
8043			27
8044			17
8045			39
8046			28
8047			12
8048			46
8049			45
8051			5
8052			31

b(4)

8053	[redacted]	28
8054		12
8055		24
8056		48
8057		28
8059		41
8060		35
8061		0
8062		19
8063		9
8070		4
8071		1
8073		0
8074		12
8075		20
8076		39
8077		23
8078		27
8094		22
8095		31
8100		52
8101		44
8104		33
8127		4

b(4)

Important Differences between Studies 18094 and 18087

	Study 18094	Study 18087
Randomization Ratio	2:2:2:1	1:1:1:1
No. of Subjects	517 (149, 148, 149, 71)	1668 (415, 420, 415, 418)
Primary Endpoints (at 12 week LOCF)	(1) Success Rate* (2) % Δ in Inflam Lesions (3) % Δ in Non-Inflam lesions (4) % Δ in Total Lesions	(1) Success Rate** (2) Δ in Inflam Lesions (3) Δ in Non-Inflam lesions
Entry Criteria	No acne nodules Allows mild acne	Not more than one acne nodule A score of "3" (Moderate) on the IGA scale.

*allows one grade improvement to be counted as success for "mild" patients who reach "clear" or almost "clear"

** 2 grade improvement needed for success for patients "clear" or "almost clear", in agreement with division recommendation

Study Populations:

The primary analysis population is defined as the intent-to-treat (ITT) population which includes all subjects who were randomized and dispensed medication. The per protocol (PP) population which excludes subjects with major protocol violations is planned as a supportive analysis to the primary analysis on the ITT population.

The table below from the sponsor's study report provides details for both studies:

Table 3: Summary of Data Sets Analyzed

	EPIDUO	Adapalene	BPO	Vehicle
Study 18094				
ITT Population	149	148	149	71
PP Population	125	116	129	51
Study 18087				
ITT Population	415	420	415	418
PP Population	319	347	346	323

Source: Sponsor's Study Report Table 8 (Study 18094) and Table 5 (Study 18087); results reproduced by reviewer.

Patient Disposition:

From the statistical reviewer report

Table 1: Subject Disposition (Study 18094)

	EPIDUO ($N = 149$)	Adapalene ($N = 148$)	Benzoyl Peroxide ($N = 149$)	Vehicle ($N = 71$)
Complete Trial	139 (93.3)	131 (88.5)	139 (93.3)	63 (88.7)
Discontinued	10 (6.7)	17 (11.5)	10 (6.7)	8 (11.3)
Lack of Efficacy	0 (0)	1 (0.7)	0 (0)	0 (0)
Adverse Event	1 (0.7)	1 (0.7)	0 (0)	0 (0)
Subject Request	4 (2.7)	10 (6.8)	7 (4.7)	7 (9.9)
Protocol Violation	2 (1.3)	1 (0.7)	0 (0)	0 (0)
Lost to Follow-up	2 (1.3)	3 (2)	3 (2)	1 (1.4)
Other	1 (0.7)	1 (0.7)	0 (0)	0 (0)

Source: Study Report Table 5; results reproduced by reviewer

There is no discernible pattern for the discontinuations from the EPIDUO arm of study 18094. The number of discontinuations in the EPIDUO arm was similar to the BP arm and less than the adapalene and vehicle arms. A total of 45 subjects discontinued from Study 18094. The most prevalent reason for subject discontinuation was due to subject request which accounted for 28 of the 45 subjects who discontinued. The overall percent of subjects that completed the trial was greater than 85% for all treatment arms.

From the statistical reviewer report

Table 2: Subject Disposition (Study 18087)

	EPIDUO ($N = 415$)	Adapalene ($N = 420$)	Benzoyl Peroxide ($N = 415$)	Vehicle ($N = 418$)
Complete Trial	347 (83.6)	363 (86.4)	372 (89.6)	347 (83.0)
Discontinued	68 (16.4)	57 (13.6)	43 (10.4)	71 (17.0)
Lack of Efficacy	1 (0.2)	2 (0.5)	0 (0.0)	1 (0.2)
Adverse Event	11 (2.7)	4 (1.0)	5 (1.2)	2 (0.5)
Subject Request	21 (5.1)	17 (4.0)	18 (4.3)	30 (7.2)
Protocol Violation	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Lost to Follow-up	31 (7.5)	32 (7.6)	19 (4.6)	34 (8.1)
Other	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)
Pregnancy	3 (0.7)	1 (0.2)	1 (0.2)	2 (0.5)

Source: Sponsor's Study Report Table 11; results reproduced by reviewer.

The percentage of discontinuations in study 18087 was higher across all arms compared with study 18094. The EPIDUO arm was comparable to placebo and higher than adapalene or BP. A total of 239 out of 1668 subjects (14.3%) discontinued from Study 18087. The most prevalent reason for subject discontinuation was due to "lost to follow-up" which accounted for 116 subjects (7.0%) who discontinued. Eleven of the 22 subjects that discontinued treatment due to an adverse event were treated with EPIDUO.

Demographics:

Study 18094

Study 18094 allowed inclusion of patients with "mild acne" based on the IGA. With regard to lesion counts, however, at least 75% of subjects in each treatment group were assessed with moderate acne at Baseline: 119 (79.9%) for Adapalene/Benzoyl Peroxide Gel, 111 (75.0%) for Adapalene Monad, 127 (85.2%) for Benzoyl Peroxide Monad, and 57 (80.3%) for Gel Vehicle. For each type of lesion, the median Baseline lesion count was similar in all treatment groups. By IGA Score, however, there was a smaller percentage of mild patients in the BPO Monad group, and a smaller percentage of severe patients in the vehicle group.

From the sponsor's study report SRE.18094, pg. 38

Table 10 Baseline Acne Characteristics, ITT Population

	Adapalene/BPO Gel N = 149		Adapalene Monad N = 148		BPO Monad N = 149		Gel Vehicle N = 71	
Baseline IGA Score								
2 = Mild	25 (16.8%)		28 (18.9%)		15 (10.1%)		13 (18.3%)	
3 = Moderate	119 (79.9%)		111 (75.0%)		127 (85.2%)		57 (80.3%)	
4 = Severe	5 (3.4%)		9 (6.1%)		7 (4.7%)		1 (1.4%)	
Baseline Lesion Count	Median	Mean	Median	Mean	Median	Mean	Median	Mean
Inflammatory	27.0	29.7	28.0	29.1	28.0	30.5	29.0	31.1
Noninflammatory	44.0	51.5	45.0	51.1	43.0	46.8	46.0	49.9
Total	78.0	81.2	75.0	80.2	74.0	77.3	78.0	81.1

Data source: RD.06.SRE.18094: Section 14.2, EFF 2.2, 3.2, 4.2, and 8.

Study 18087

For study 18087 almost all subjects (1663, 99.8%) had IGA Scores assessed as moderate acne at Baseline due to inclusion criteria. For each type of lesion, the median Baseline lesion counts were similar in all treatment groups.

From the sponsor's study report SRE.18087, pg.82

Table 7 Summary of Subject Baseline Acne Characteristics (ITT)

	Adapalene/Benzoyl Peroxide Gel N = 415		Adapalene Gel N = 420		Benzoyl Peroxide Gel N = 415		Gel Vehicle N = 418[a]		Total N = 1668	
Investigator Global Assessment, n (%)										
3 = Moderate	415 (100.0)		420 (100.0)		414 (99.8)		414 (99.5)		1663 (99.8)	
4 = Severe	0		0		1 (0.2)		2 (0.5)		3 (0.2)	
Baseline Lesion Count	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)
Inflammatory	27.0	29.4 (7.98)	27.0	29.7 (8.21)	27.0	29.4 (8.33)	27.0	29.4 (8.22)	27.0	29.5 (8.18)
Noninflammatory	44.0	51.6 (19.30)	47.0	52.3 (19.04)	46.0	52.0 (19.10)	46.0	51.5 (18.99)	46.0	51.9 (19.10)
Total	76.0	81.1 (22.04)	79.0	82.1 (21.27)	76.0	81.6 (22.13)	76.0	81.0 (21.56)	76.0	81.4 (21.73)

[a]Subject 8020/92381 had no baseline or no post-baseline IGA, and Subject 8020/92007 had no baseline, but did have a post-baseline IGA.
Data Source: RD.08.SRE.18087, Section 14.1, SUB 4.1

For a full table of baseline demographics of the safety population see section 7.2.1, Table 7 **"Demographic and Baseline Characteristics, Safety Population, SRE.18094 and SRE.18087 Combined, and SRE.18089"**

Outcome Efficacy:

Study 18094- Outcome Efficacy

In the review of the protocol for Study 18094 it was communicated to the sponsor that the definition of success using the IGA should be in agreement with the Division. The protocol lists the definition of treatment success based on the IGA as subjects with an IGA score of `Clear' or `Almost Clear'. However, the enrollment criteria for study 18094 allowed for subjects to enroll with a baseline IGA score of `Mild' in which case based upon the protocol definition of IGA success, subjects enrolling with a `Mild' IGA score can have a one grade improvement to be considered a success. Typically the Division requests subjects enrolling with `Mild' IGA scores to reach `Clear' to be considered a treatment success. As such, the statistician's review considers multiple definitions of treatment success which are listed below.

Clear' or `Almost Clear': Subjects with an IGA score of `Clear' or `Almost Clear' at the end of treatment visit are considered a treatment success.

Two Grade Improvement: Subjects who have a two grade improvement from their baseline IGA score are considered a treatment success.

Intersecting Definition: Subjects must have a two grade improvement from the baseline IGA score AND reach a score of `Clear' or `Almost Clear' to be considered a treatment success.

Using the above definitions of treatment success based on the IGA scale, Table 4 from the statistician's review depicts the efficacy results for Study 18094. This table shows that for each definition of IGA success, EPIDUO was statistically superior to each monad and the vehicle at the @ = 0:05 significance level when using CMH stratified by analysis center.

Table 4 from the statistician's review

Table 4: Investigator Global Results (ITT-LOCF)

	EPIDUO ($N = 149$)	Adapalene ($N = 148$)	BPO ($N = 149$)	Vehicle ($N = 71$)
Clear or Almost Clear[†]				
Success (%)	41 (27.5)	23 (15.5)	23 (15.4)	7 (9.9)
p-value	-	0.0079	0.0034	0.0015
Two Grade Improvement[*]				
Success (%)	33 (22.1)	19 (12.8)	18 (12.1)	4 (5.6)
p-value	-	0.0309	0.0056	0.0016
Intersecting Definition[*]				
Success (%)	32 (21.5)	18 (12.2)	18 (12.1)	4 (5.6)
p-value	-	0.0291	0.0088	0.0023

[†] Source: Sponsor's Study Report Table 12; results reproduced by reviewer.

[*] Source: Reviewer Analysis.

Regardless of the analysis used, with regard to IGA, EPIDUO was statistically significantly better than its monads and vehicle.

A summary of the change as well as the percent reduction in inflammatory lesion counts is provided in Table 6 from the statistician's review. The division prefers the absolute change in lesions because it lessens the impact of outliers; therefore the p values shown are based on the absolute change.

Table 6: Change in Inflammatory Lesion Counts (ITT-LOCF): 18094

	EPIDUO ($N = 149$)	Adapalene ($N = 148$)	BPO ($N = 149$)	Vehicle ($N = 71$)
Mean Change	-16.0	-11.4	-10.5	-9.5
Mean Percent Change	-52.4	-39.9	-35.8	-31.8
p-value	-	.0012	< 0.001	< 0.001

Source: Reviewer's analysis using an ANCOVA model with main effects only on the unranked data.

With regard to change in inflammatory lesions from baseline, EPIDUO was statistically significantly better than its monads and vehicle.

A summary of the change as well as the percent reduction in non-inflammatory lesion counts for study 18094 is provided in Table 7 from the statistician's review.

Table 7: Change in Non-Inflammatory Lesion Counts (ITT-LOCF): 18094

	EPIDUO ($N = 149$)	Adapalene ($N = 148$)	BPO ($N = 149$)	Vehicle ($N = 71$)
Mean Change	-23.4	-15.2	-13.7	-13.2
Mean Percent Change	-45.9	-29.6	-32.2	-27.8
p-value	-	0.0001	.0001	0.0003

Source: Reviewer's analysis using an ANCOVA model with main effects only on the unranked data.

With regard to change in non-inflammatory lesions from baseline, EPIDUO was statistically significantly better than its monads and vehicle.

A summary of the change as well as the percent reduction in total lesion counts is provided in Table 8 from the statistician's review.

Table 8: Change in Total Lesion Counts (ITT-LOCF): 18094

	EPIDUO ($N = 149$)	Adapalene ($N = 148$)	BPO ($N = 149$)	Vehicle ($N = 71$)
Mean Change	-39.3	-26.5	-24.1	-22.6
Mean Percent Change	-48.5	-34.0	-33.3	-29.7
p-value	-	< 0.001	< 0.001	< 0.001

Source: Reviewer's analysis using an ANCOVA model with main effects only on the unranked data.

With regard to change in total lesions from baseline, EPIDUO was statistically significantly better than its monads and vehicle.

Outcome Efficacy

Study 18087- Outcome Efficacy

In the analysis of percent success on IGA, EPIDUO was superior to each monad and its vehicle in Study 18087. Success is defined for subjects that receive an IGA score of 0 (clear) or 1 (almost clear) at week 12. To test the superiority of EPIDUO to the other three treatment arms, a Cochran-Mantel-Haenszel (CMH) test was carried out with adjustments for analysis center. The results of the CMH test are provided in Table 5.

Table 5 from the statistician's review

Table 5: Investigator Global Results (ITT-LOCF)

	EPIDUO ($N = 415$)	Adapalene ($N = 420$)	BPO ($N = 415$)	Vehicle ($N = 417$)
Success (%)	125 (30.1)	83 (19.8)	92 (22.2)	47 (11.3)
p-value	-	$< .001$	0.0062	$< .001$

Source: Sponsor's Study Report Tables 10 and 11; results reproduced by reviewer.

Based on the CMH tests, EPIDUO is superior to each monad and vehicle in Study 18087 at the statistical significance level of @ = 0:05.

Efficacy results for inflammatory lesion counts are listed in Table 9. Results are provided for both the ranked and unranked data. The p-value on the ranked data is above the @ = 0:05 level for the comparison of EPIDUO to benzoyl peroxide though the p-value is 0.0387 for the unranked data.

Table 9 from the statistician's review

Table 9: Change in Inflammatory Lesion Counts (ITT-LOCF): 18087

	EPIDUO ($N = 415$)	Adapalene ($N = 420$)	BPO ($N = 415$)	Vehicle ($N = 418$)
Inflammatory Lesion Counts				
Mean Change	-15.4	-12.3	-13.7	-8.7
Mean Percent Change	-53.4	-41.7	-47.6	-30.2
p-value†	-	< 0.001	0.068	< 0.001
p-value‡	-	< 0.001	0.0387	< 0.001

† Sponsor's analysis using a main effects model with the ranked data; results reproduced by the reviewer.

‡ Reviewer's analysis using a main effects model the the unranked data.

With regard to change in inflammatory lesions, EPIDUO is superior to the adapalene monad and vehicle in Study 18087 at the statistical significance level of @ = 0:05. With regard to change in inflammatory lesions, EPIDUO does not demonstrate statistically significant superiority over the BPO monad for the ranked data. This is discussed further under "Discussion of Findings/Conclusions".

A summary of the change as well as the percent reduction in non-inflammatory lesion counts is provided in Table 10.

Table 10 from the statistician's review

Table 10: Change in Non-Inflammatory Lesion Counts (ITT-LOCF): 18087

	EPIDUO ($N = 415$)	Adapalene ($N = 420$)	BPO ($N = 415$)	Vehicle ($N = 418$)
Mean Change	-24.6	-21.0	-19.2	-11.3
Mean Percent Change	-48.1	-40.8	-37.2	-23.2
p-value†	-	0.048	< 0.001	< 0.001
p-value‡	-	0.0009	0.0002	< 0.001

† Sponsor's analysis using a main effects model with the ranked data; results reproduced by the reviewer.

‡ Reviewer's analysis using a main effects model with the the unranked data.

With regard to change in non-inflammatory lesions, EPIDUO is superior to the adapalene monad, the BPO monad and vehicle in Study 18087 at the statistical significance level of @ = 0:05.

A summary of the change as well as the percent reduction in total lesion counts is provided in Table 11. The table also provides p-values for testing the main treatment effect for a model with the main effects only.

Table 11 from the statistician's review

Table 11: Change in Total Lesion Counts (ITT-LOCF): 18087

	EPIDUO ($N = 415$)	Adapalene ($N = 420$)	BPO ($N = 415$)	Vehicle ($N = 418$)
Mean Change	-39.9	-33.3	-33.0	-20.0
Mean Percent Change	-50.	-41.3	-41.2	-26.1
p-value	-	0.0003	0.0004	< 0.001

Source: Reviewer's analysis using an ANCOVA model with main effects only on the unranked data.

With regard to change in number of total lesions, EPIDUO was statistically superior to each of its monads and vehicle.

See statistician's review for results in PP population and sensitivity analyses

Outcome of Safety Assessments:

Study 18094 - Safety Assessments:

A safety assessment was conducted for all subjects at Baseline and every subsequent visit. The safety parameters are the record of adverse events and the recording of local tolerability which is graded as below from the sponsor's protocol 18094, page 36

Erythema, scaling, dryness, and stinging/burning will be graded at Baseline and each post-baseline visit as follows:

Erythema: abnormal redness of the skin.

None	0	No erythema
Mild	1	Slight pinkness present
Moderate	2	Definite redness, easily recognized
Severe	3	Intense redness

Scaling: abnormal shedding of the stratum corneum.

None	0	No scaling
Mild	1	Barely perceptible shedding, noticeable only on light scratching or rubbing
Moderate	2	Obvious but not profuse shedding
Severe	3	Heavy scale production

Dryness: brittle and/or tight sensation.

None	0	No dryness

With regard to adverse events in study 18094 the incidence was comparable between Adapalene/Benzoyl Peroxide Gel and Adapalene Gel but slightly higher compared to Benzoyl Peroxide Gel and Gel Vehicle. The number of subjects with AEs was comparable across the arms of the study. There were no significant non-skin related adverse events felt to be related to the medication demonstrated.

Most of the signs and symptoms of local tolerability were mild or moderate in severity in study 18094. The incidence of the signs and symptoms of local tolerability worse than baseline were highest at Week 1 of treatment and subsided thereafter.

See section 7, Safety Review for detailed results of safety assessments.

Outcome of Safety Assessments:

Study 18087 - Safety Assessments:

A safety assessment was to be conducted for all subjects at Baseline and every subsequent visit. The safety parameters were Adverse Events and Local Tolerability Assessments. Similar to study 18094, adverse events in study 18087 were comparable between Adapalene/Benzoyl Peroxide Gel and Adapalene Gel but slightly higher compared to Benzoyl Peroxide Gel and Gel Vehicle. The number of subjects with AEs was also comparable across the arms of the study. There were no significant non-skin related adverse events felt to be related to the medication demonstrated.

Local Tolerability Assessment parameters (Erythema, Scaling, Dryness, and Stinging/Burning) were evaluated on a 4-point scale with "0" = None, "1" = Mild, "2" = Moderate, "3" = Severe at each visit. Overall, the incidences of erythema, scaling, dryness, and stinging/burning were higher in the Adapalene/Benzoyl Peroxide Gel group than in other treatment groups. However, most higher Local Tolerability Scores occurred early in the study, subsided generally after Week 1 or 2, and decreased over time with continued use of study medication. Additionally, the severity was mostly Mild or Moderate with very few Severe events.

See section 7, Safety Review for detailed results of safety assessments.

Discussion of Findings/Conclusions:

In study 18094 Adapalene/Benzoyl Peroxide Gel had a clinically superior and statistically significantly higher Success Rate (p is less than or equal to 0.008 for all analyses at Week 12 LOCF, ITT) when compared to either monad or Gel Vehicle. In study 18094 with regard to change in inflammatory lesions from baseline, change in non-inflammatory lesions from baseline, and change in total lesions from baseline, EPIDUO was statistically significantly better than its monads and vehicle.

For Success Rate in study SRE.18087, all comparisons of Adapalene/Benzoyl Peroxide Gel to Monads and to Gel Vehicle were significant ($p<0.006$). In study 18087 the changes in non-inflammatory lesion counts from baseline to week 12 (LOCF) for subjects treated with Adapalene/Benzoyl Peroxide Gel for all comparisons to Monads and Gel Vehicle were significant (p is less than or equal to 0.048). The changes in inflammatory lesion counts from baseline to week 12 (LOCF) for subjects treated with Adapalene/Benzoyl Peroxide Gel in comparison to Adapalene Gel, and Gel Vehicle were significant ($p<0.001$). The comparison of Adapalene/Benzoyl Peroxide Gel was not significantly different from Benzoyl Peroxide Gel ($p=0.068$).

The designs of both pivotal studies were generally adequate to assess the safety of the product for its intended use. Topical safety was adequately evaluated and included assessment for adverse events and local tolerance assessments. The safety profile of Adapalene/Benzoyl

Peroxide Gel appears to be acceptable and differs only slightly from the monads adapalene gel and benzoyl peroxide in that it is somewhat more irritating.

Overall the weight of evidence of the superiority of EPIDUO Gel over its monads is convincing. The only failure to reach statistical significance was for inflammatory lesions compared with benzoyl peroxide in study 18087 and this can be balanced by the decisive superiority in the majority of the other comparisons in 18087 and in all of the comparisons in 18094.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The indication sought by the applicant is for topical application in the treatment of acne vulgaris in patients 12 years of age and older.

6.1.1 Methods

The efficacy evaluation of Adapalene 0.1%/Benzoyl Peroxide 2.5% is based on detailed review of 2 pivotal well-controlled double-blind, 12-week, multi-center, active and vehicle-controlled studies SRE.18087 and SRE.18094, and one supporting open-label long-term (one year) safety and efficacy study SRE.18089. See section 5.3 for details on the individual protocols.

6.1.2 Demographics

Study 18094

Overall, 59.8% (309/517) of subjects were males, the mean age was 16.4 years, and ranged from 12 to 56 years. 71.6% (370/517) of subjects were Caucasian. Of the remaining subjects (13.2%, 68) were Hispanic; 57 (11.0%) were Black, 17 (3.3%) were other races, and 5 (1.0%) were Asian. At Baseline, all groups were comparable with respect to gender, age, race distribution, and skin phototype.

Study 18087

The mean age of subjects was 18.2 years (ranged 12 to 58 years) and approximately half were female (51.3%). The majority of subjects were Caucasian (1082; 64.9%) and the remainder were, Black (277; 16.6%), Hispanic (270; 16.2%) other races (22; 1.3%) or Asian (17; 1.0%). At Baseline, all groups were comparable with respect to gender, age, race distribution, and skin phototype.

For lesion count demographics see section 5.3 Discussion of Individual Studies under "demographics"

6.1.3 For full table of baseline demographics of safety population see table #7 under Section 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

6.1.4 Patient Disposition

See section 5.3 Discussion of Individual Studies under "patient disposition"

6.1.5 Analysis of Primary Endpoint(s)

As discussed in section 5.3 under the heading "Outcome Efficacy" the primary endpoints for study 18094 differed from those of study 18087 and were not the endpoints recommended by the division.

The primary efficacy criteria for study 18094 were

- the percentage of subjects graded as "Clear" or "Almost Clear" according to the dichotomized Investigator's Global Assessment
- percent change from baseline of facial non-inflammatory, inflammatory lesion counts and total lesion counts

The following IGA Scale from the sponsor's study report was used in study 18094

Table 4 Investigator's Global Assessment of Acne Severity

INVESTIGATOR'S GLOBAL ASSESSMENT			
Success	0	Clear	Residual hyperpigmentation and erythema may be present.
	1	Almost Clear	A few scattered comedones and a few (less than five) small papules.
	2	Mild	Easily recognizable; less than half the face is involved. Some comedones and some (five or more) papules and pustules.
	3	Moderate	More than half of the face is involved. Many comedones, papules and pustules.
	4	Severe	Entire face is involved. Covered with comedones, numerous papules and pustules and few nodules and cysts.
	5	Very Severe	Highly inflammatory acne covering the face; with nodules and cysts present.

Data source: Appendix 16.1.1., Protocol and Amendments

The co-primary endpoints in study 18087 were discussed with the division and agreed upon during the review of the protocol:

- Success rate, the percentage of subjects with "0 = Clear" or "1 = Almost Clear" on the Investigators Global Assessment (0 to 4 scale) at week 12
- Changes in inflammatory and non-inflammatory lesion counts from baseline to week 12

The following IGA Scale from the sponsor's study report was used in study 18087

Table 3 Investigator's Global Assessment of Acne Severity

Investigator's Global Assessment Scale			
Success	0	"Clear"	Residual hyperpigmentation and erythema may be present.
	1	"Almost Clear"	A few scattered comedones and a few small papules.
	2	"Mild"	Easily recognizable; less than half the face is involved. Some comedones and some papules and pustules.
	3	"Moderate"	More than half of the face is involved. Many comedones, papules and pustules. One nodule may be present.
	4	"Severe"	Entire face is involved, covered with comedones, numerous papules and pustules, and few nodules and cysts.

Data Source: Appendix 16.1.1., Protocol and Amendments

In the draft "Guidance for Industry Acne Vulgaris: Developing Drugs for Treatment" the agency recommends combining the ordinal global assessment scale and lesion counts as "co-primary endpoints" in order to allow for a balanced approach towards the evaluation of acne severity. The IGA recommended in the guidance is a 5 severity grade scale to be dichotomized to success or failure using clear or almost clear (Grades 0 or 1) as success.

In the draft "Guidance for Industry Acne Vulgaris: Developing Drugs for Treatment" success is defined as "Clear" (Grade 0) or "Almost clear" (Grade 1) at the prespecified primary time point. For patients whose baseline score is Grade 2, the clinically meaningful criterion for IGA success is achieving a score of Grade 0 at the prespecified primary time point because of limitations inherent to an ordinal scale.

In the draft "Guidance for Industry Acne Vulgaris: Developing Drugs for Treatment" the agency recommends noninflammatory and inflammatory acne lesion counts as co-primary endpoints along with the IGA. When counting facial acne lesions, it is important that all lesions be counted, including those present on the nose.

The primary endpoints in study 18087, for the most part, conform to these specifications. The only exception is that lesion counts were performed excluding the nose. The primary endpoints in study 18094 deviate from these specifications in the following ways:

- The use of a 6 severity grade scale with a "very severe" category added.
- The inclusion of mild patients (grade 2) with success defined as a one grade improvement.
- The use of percentage change rather than absolute change in lesion counts as endpoints.
- The exclusion of the nose from lesions counts when they were performed.

See section 5.3 Discussion of Individual Studies under Outcome Efficacy for detailed discussion of results

6.1.6 Analysis of Secondary Endpoints(s)

Percent changes of the lesion counts are the only secondary endpoints intended for labeling claims. In the review of SN054 (stamp date: 04/20/2007) the Division agreed that these secondary endpoints could be included in the label if the primary endpoint for change in lesion counts meets statistical criteria without multiplicity adjustment. Point estimates for the percent reduction in lesion counts are provided in Tables 6, 7, and 8 for Study 18094 and Tables 9, 10, and 11 for Study 18087 in section 5.3 of this review.

6.1.7 Other Endpoints

The sponsor studied tertiary efficacy parameters such as the full IGA scale evaluation and the Subject's Assessment of Acne at Week 12 (LOCF, ITT) [ ] b(4)

6.1.8 Subpopulations

The study database was not large enough to assess whether there were statistically significant differences in effects among age, gender or race subgroups. There were no trends seen that indicated statistically significant effects of these subgroups on efficacy or adverse events. The data from the sponsor's study report of 18094 is presented in the table below.

Table 21 Success Rate by Gender, Race, and Age, ITT Population

Success Rate at Week 12 (LOCF)	Adapalene/BPO Gel		Adapalene Monad		BPO Monad		Gel Vehicle	
	N	n	N	n	N	n	N	n
All subjects	149	41 (27.5%)	148	23 (15.5%)	149	23 (15.4%)	71	7 (9.9%)
Gender								
Male	87	20 (23.0%)	86	13 (15.1%)	96	11 (11.5%)	40	4 (10.0%)
Female	62	21 (33.9%)	62	10 (16.1%)	53	12 (22.6%)	31	3 (9.7%)
Race								
Caucasian	101	27 (26.7%)	103	12 (11.7%)	114	18 (15.8%)	52	4 (7.7%)
Non-Caucasian	48	14 (29.2%)	45	11 (24.4%)	35	5 (14.3%)	19	3 (15.8%)
Age								
Age range: 12 – 17 yrs	121	34 (28.1%)	116	18 (15.5%)	116	16 (13.8%)	48	2 (4.2%)
Age range: 18 – 64 yrs	28	7 (25.0%)	32	5 (15.6%)	33	7 (21.2%)	23	5 (21.7%)

Week 12 LOCF (Endpoint): The last available data observed during the study. Baseline value was used if no post-Baseline data were available.
Data source: RD.06.SRE.18094, Section 14.2, Table EFF 1.2, Gender: 12.1.1, 12.1.2 Race: 12.2.1, 12.2.2 Age: 12.3.1, 12.3.2

Most subjects in both studies were Caucasian. There was a slight trend towards better results in non-caucasians in study 18094. Although treatment effects were generally similar, female subjects tended to have slightly better overall results than males in study 18094. In 18094, Adult subjects (18 and older) generally had similar results to adolescent subjects (age 10 – 17), with the exception of BPO and vehicle monads where the adults did better.

The data from the sponsor's study report of 18087 is presented in the table below.

Table 21 **Success Rate by Gender, Race, and Age at Week 12 (LOCF) ITT Population**

Success Rate	Adapalene/ Benzoyl Peroxide Gel		Adapalene Gel		Benzoyl Peroxide Gel		Gel Vehicle	
	N	n (%)	N	n (%)	N	n (%)	N	N (%)
All subjects	415	125 (30.1)	420	83 (19.8)	415	92 (22.2)	417*	47 (11.3)
Gender								
Male	205	53 (25.9)	203	35 (17.2)	208	43 (20.7)	196	20 (10.2)
Female	210	72 (34.3)	217	48 (22.1)	207	49 (23.7)	221	27 (12.2)
Race								
Caucasian	273	81 (29.7)	281	50 (17.8)	258	58 (22.5)	269	29 (10.8)
Non-Caucasian	142	44 (31.0)	139	33 (23.7)	157	34 (21.7)	148	18 (12.2)
Age								
Age range: 12 – 17 yrs	265	72 (27.2)	279	45 (16.1)	273	57 (20.9)	273	31 (11.4)
Age range: 18 – 64 yrs	150	53 (35.3)	141	38 (27.0)	142	35 (24.6)	144	16 (11.1)

Week 12 LOCF (Endpoint): The last available data observed during the study. Baseline value was used if no post-Baseline data were available.
Data Source: RD.06.SRE.18087, Section 14.2, Table EFF 5.1, Gender: Table EFF 15.1.1, Table EFF 15.1.2 Race: Table EFF 15.2.1, Table EFF 15.2.2 Age: Table EFF 15.3.1, Table EFF 15.3.2

There was a slight trend towards better results in non-caucasians in study 18087 with the exception of the BPO monad where they were equal. Although treatment effects were generally similar, female subjects tended to have slightly better overall results than males in study 18087. In 18087, Adult subjects (18 and older) generally had better results compared to adolescent subjects (age 10 – 17), with the exception of the vehicle monad where the adolescents did better.

6.1.9 Analysis of Clinical Information Relevant to Dosing Recommendations

In study SRE.2674 a left/right split comparison dose-finding study, Adapalene0.1%/BP2.5% was compared to Adapalene0.1%/BP5% in fixed combination, as well as to marketed BP formulations ranging from 2.5% to 10%. The combination product with BP2.5% was tolerated well with a similar side effect profile to both 2.5 and 5% BP alone. The combination product with BP5% induced significantly more irritation than both 5 and 10% BP alone. The lower dose combination was therefore selected for further development. This was the only study submitted for review that assessed the dose response relationship. No efficacy assessment was performed during this study.

For further details on this study please see section 7.5.1 Dose Dependency for Adverse Events

6.1.10 Discussion of Persistence of Efficacy and/or Tolerance Effects

This issue was not addressed in the development program for EPIDUO. The only long term study, 18089 was for one year duration of use but was open label.

6.1.11 Additional Efficacy Issues/Analyses

There were no additional efficacy issues identified or analyses performed.

7 Review of Safety

Safety Summary

An adequate number of subjects were exposed to Adapalene0.1%/Benzoyl Peroxide 2.5% under the proposed dosing regimen to permit characterization of its safety for the intended use of once daily. A total of 1401 subjects have been exposed to adapalene/BPO gel in this development program. A total of 361 subjects (79.9%) were treated for at least 6 months (180 days or more), and 194 subjects (42.9%) were treated for 1 year (at least 360 days). In the long term safety and efficacy study SRE.18089, the mean total medication use was 209.5g, corresponding to a mean daily medication use of 0.69 g/day.

The designs of the Phase 3 studies were generally adequate to assess the safety of the product for its intended use. Topical safety was adequately evaluated in the development program and included assessment for local adverse events and formal dermal safety studies. No deaths occurred in the clinical development program of Adapalene/Benzoyl Peroxide Gel.

In looking at all adverse events in the pivotal studies combined, the incidence was comparable between Adapalene/Benzoyl Peroxide Gel and Adapalene Gel but slightly higher compared to Benzoyl Peroxide Gel and Gel Vehicle. The number of subjects with AEs was comparable among the groups (35.3%, 37.3%, 28.2%, and 27.8% for Adapalene/Benzoyl Peroxide Gel, Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle, respectively). There were no significant non-skin related adverse events felt to be related to the medication demonstrated in the development program.

Adapalene is a widely marketed acne product and its adverse event profile is reasonably well understood. Benzoyl Peroxide has been used as an effective acne treatment for over 40 years. The common side effects for both of these products include skin irritation, dryness, redness, and peeling and are predictable.

Most of the signs and symptoms of local tolerability were mild or moderate in severity. The incidence of the signs and symptoms of local tolerability worse than baseline were highest at

Week 1 of treatment and subsided thereafter in both the pivotal studies and in the long term safety study. Most of the Adverse Events leading to discontinuation were caused by the well known irritative properties of adapalene and benzoyl peroxide. Labeling is adequate to address these safety concerns.

The numbers of subjects in the phototoxicity study (25 instead of 30), photosensitization study (33 instead of 45), and cumulative irritation study (25 instead of 35) are less than those typically recommended by the Division. The number of subjects was adequate to assess safety.

A high incidence of sensitization was found for Adapalene/Benzoyl Peroxide Gel and Benzoyl Peroxide 2.5% Gel. The presence of adapalene in the fixed-combination did not increase the sensitization potential of benzoyl peroxide alone. There was an unusually high rate of sensitization to both BP 2.5% alone and to the combination product (most likely due to the presence of BP 2.5% as a component of that combination product) possibly due to the occlusive conditions of the testing. These findings are not dissimilar from what was found in a literature search of provocative testing with benzoyl peroxide under occlusive conditions. This is in contrast to the lack of a signal in the irritancy study where semi-occlusive conditions were used. It is also in marked contrast to the lack of a signal in the clinical trials. This will need to be addressed in labeling.

The gelling agent, Simulgel 600 PHA, a novel excipient, was tested separately in studies HICV 97.271 (assessment of acute irritation potential), HICV 97.270 (assessment of acute irritation potential), le 491/98.4213 (assessment of cutaneous tolerance after repeated administration) and If 037/99.0238 (assessment of cutaneous tolerance and sensitization potential) and integrally in Adapalene/Benzoyl Peroxide Gel and no irritancy or sensitization signal has been detected. These studies, all performed in healthy subjects, were included in this NDA but were not reviewed in depth.

The four month safety update report was reviewed and did not reveal new information that would effect labeling.

7.1 Methods

7.1.1 Clinical Studies Used to Evaluate Safety

Deaths, serious adverse events, discontinuations due to adverse events, and clinically important adverse events were considered from all clinical studies.

In total ten clinical trials with Adapalene/Benzoyl Peroxide Gel were presented by the sponsor:

- One dose finding study in healthy subjects (SRE.2674)
- Four dermal safety studies in healthy subjects (SRE.2687, SRE.2683, SRE.2681, and SRE.2682).

- Two pharmacokinetic studies in subjects with acne vulgaris (SRE.2685 and SRE.18097).
- Two well-controlled 12-week efficacy and safety studies (SRE.18087 and SRE.18094).
- One open-label, long-term safety and efficacy study (SRE.18089).

7.1.2 Adequacy of Data

An adequate number of subjects were exposed to Adapalene0.1%/Benzoyl Peroxide 2.5% under the proposed dosing regimen to permit characterization of its safety for the intended use of once daily. A total of 1401 subjects have been exposed to adapalene/BPO gel in this development program. The designs of the Phase 3 studies were generally adequate to assess the safety of the product for its intended use. Topical safety was adequately evaluated in the development program and included assessment for local adverse events and formal dermal safety studies. No deaths occurred in the clinical development program of Adapalene/Benzoyl Peroxide Gel. Systemic safety was adequately evaluated in the development program and included the collection of systemic adverse event data. There were no significant non-skin related adverse events felt to be related to the medication demonstrated in the development program.

7.1.3 Pooling Data Across Studies to Estimate and Compare Incidence

The safety data collected in the two well controlled 12-week efficacy and safety studies (SRE.18094 and SRE.18087) were integrated to support overall safety of Adapalene/Benzoyl Peroxide Gel in comparison to the monads (Adapalene Gel, Benzoyl Peroxide Gel) and Gel Vehicle. The safety data are integrated from a total of 2185 subjects: Adapalene/Benzoyl Peroxide Gel (N=564), Adapalene Gel (N=568), Benzoyl Peroxide Gel (N=564) , and Gel Vehicle (N=489). The incidence of nondermatological adverse events was comparable between the treatment groups (25.9%, 30.3%, 23.4%, and 24.1% for Adapalene/Benzoyl Peroxide Gel, Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle, respectively).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The fixed-combination of Adapalene/Benzoyl Peroxide Gel is not marketed in any region.

A total of 1401 subjects have been exposed to adapalene/BPO gel in this development program.

- 31 subjects in the dose finding study in healthy subjects (SRE.2674)
- 334 subjects in the dermal safety studies in healthy subjects (SRE.2687, SRE.2683, SRE.2681, andSRE.2682)
- 20 subjects in the two pharmacokinetic studies in subjects with acne vulgaris (SRE.2685 and SRE.18097)

- 564 subjects in the two well-controlled 12-week efficacy and safety studies (SRE.18087 and SRE.18094)
- 452 subjects in the one open-label, long-term safety and efficacy study (SRE.18089)

A total of 1036 of these subjects had acne vulgaris i.e. the indication for which this product is intended, there were 365 healthy subjects.

Acne is predominately a disease of adolescents and young adults. The mean age of the subjects in the pivotal studies (18097 and 18094) was 17.8 years (range 12 to 58 years). The mean age was 18.3 years (range 12 to 50 years) in long-term safety study SRE.18089. The proportion of subjects 12 to 17 years of age was 68.3% (1492 of 2185) in the combined pivotal studies and 66.2% (299 of 452) in the long term safety study. The majority of subjects were Caucasian in the two well-controlled studies combined (66.5%) and also in the open-label long term safety and efficacy study (76.3%).

Table 7 Demographic and Baseline Characteristics, Safety Population, SRE.18094 and SRE.18087 Combined, and SRE.18089 From the sponsor's Section 2.7.4 (pg.21)

	Well Controlled Studies (SRE.18094 + SRE.18087) 12 Weeks					Open-label SRE.18089 1 Year
Category	Adapalene/ Benzoyl Peroxide Gel N = 564 n (%)	Adapalene Gel N = 568 n (%)	Benzoyl Peroxide Gel N = 564 n (%)	Gel Vehicle N = 489 n (%)	Total N = 2185 n (%)	Adapalene/ Benzoyl Peroxide Gel N = 452 n (%)
Gender						
Male	292 (51.8)	289 (50.9)	304 (53.9)	236 (48.3)	1121 (51.3)	222 (49.1)
Female	272 (48.2)	279 (49.1)	260 (46.1)	253 (51.7)	1064 (48.7)	230 (50.9)
Age (Year)						
Mean	18.1	17.5	17.9	17.8	17.8	18.3
S.D.	6.67	5.15	6.13	5.86	5.98	6.62
Median	16.0	16.0	16.0	16.0	16.0	16.0
Min, Max	12, 58	12, 41	12, 56	12, 50	12, 58	12, 50
Age Categories						
12 to 17	386 (68.4)	395 (69.5)	389 (69.0)	322 (65.8)	1492 (68.3)	299 (66.2)
18 to 64	178 (31.6)	173 (30.5)	175 (31.0)	167 (34.2)	693 (31.7)	153 (33.8)
Race						
Caucasian	374 (66.3)	384 (67.6)	372 (66.0)	322 (65.8)	1452 (66.5)	345 (76.3)
Black	84 (14.9)	84 (14.8)	91 (16.1)	75 (15.3)	334 (15.3)	53 (11.7)

Asian	5 (0.9)	5 (0.9)	6 (1.1)	6 (1.2)	22 (1.0)	10 (2.2)
Hispanic	90 (16.0)	84 (14.8)	83 (14.7)	81 (16.6)	338 (15.5)	31 (6.9)
Other	11 (2.0)	11 (1.9)	12 (2.1)	5 (1.0)	39 (1.8)	13 (2.9)
Skin Photo Type						
I	18 (3.2)	18 (3.2)	23 (4.1)	11 (2.2)	70 (3.2)	12 (2.7)
II	123 (21.8)	124 (21.8)	112 (19.9)	107 (21.9)	466 (21.3)	105 (23.2)
III	199 (35.3)	197 (34.7)	190 (33.7)	173 (35.4)	759 (34.7)	162 (35.8)
IV	104 (18.4)	119 (21.0)	113 (20.0)	111 (22.7)	447 (20.5)	87 (19.2)
V	71 (12.6)	61 (10.7)	76 (13.5)	51 (10.4)	259 (11.9)	61 (13.5)
VI	49 (8.7)	49 (8.6)	50 (8.9)	36 (7.4)	184 (8.4)	25 (5.5)

The majority of the inclusion criteria for subjects in the two 12-week well-controlled efficacy and safety Studies (SRE.18094 and SRE.18087) and the 1-year open-label, long-term safety and efficacy study (SRE.18089) were similar. Baseline median Inflammatory, Noninflammatory, and Total lesion counts were similar in the three studies.

Table 8 Baseline Acne Characteristics, Safety Population, SRE.18094 and SRE.18087 Combined, and SRE.18089

	Well controlled Studies (SRE.18094 and SRE.18087) 12 Weeks										Open Label SRE.18089 1 Year	
Baseline Investigator's Global Assessment Score	Adapalene/ Benzoyl Peroxide Gel N = 564 n (%)		Adapalene Gel N = 568 n (%)		Benzoyl Peroxide Gel N = 564 n (%)		Gel Vehicle N = 489 n (%)		Total N = 2185 n (%)		Adapalene/ Benzoyl Peroxide Gel N = 452 n (%)	
1 = none	0		0		0		0		0		ND	
2 = mild	25 (4.4)		28 (4.9)		15 (2.7)		13 (2.7)		81 (3.7)		ND	
3 =moderate	534 (94.7)		531 (93.5)		541 (95.9)		471 (96.7)		2077 (95.1)		ND	
4 = severe	5 (0.9)		9 (1.6)		8 (1.4)		3 (0.6)		25 (1.1)		ND	
Baseline Lesion Count	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean	Median	Mean
Inflammatory	27	29.5	27	29.5	27	29.7	27	29.7	27	29.6	27	29.6
Noninflammatory	44	51.6	46	52.0	45	50.7	46	51.3	45	51.4	42	47.8
Total	76	81.2	77	81.6	76	80.4	77	81.0	76	81.0	72	77.3

Data source: ISS Appendix 1, Table 5.

From Adapalene/Benzoyl Peroxide Gel Section 2.7.4 Summary of Clinical Safety (pg. 23)

As of 28 September 2007, an estimated number of more than ——— patients have been exposed to the substance adapalene (0.1% gel, cream or solution). More than ——— patients have been exposed to benzoyl peroxide marketed by Galderma . b(4)

An adequate number of subjects were exposed to the new product under the proposed dosing regimen to permit characterization of its safety for the intended use of once daily. The designs of the Phase 3 studies were generally adequate to assess the safety of the product for its intended use. Topical safety was adequately evaluated in the development program and included assessment for local adverse events and formal dermal safety studies. The number of subjects in each dermal safety study were less than those recommended but was adequate to assess safety. Systemic safety was adequately evaluated in the development program and included the collection of systemic adverse event data. Sufficient numbers of subjects were exposed to the product for the requisite time periods as recommended in the ICH EIA guideline. There is a body of information available for the active ingredients marketed individually as well. The development program did not raise any new safety concerns.

Dose and Duration of Treatment in Long Term Safety and Efficacy Study

In the long term safety and efficacy study SRE.18089, the mean total medication use was 209.5g, corresponding to a mean daily medication use of 0.69 g/day. The mean daily medication use in the long-term study was comparable to the mean daily medication use (0.7 g/day) in the two well controlled pivotal studies. A total of 361 subjects (79.9%) were treated for at least 6 months (180 days or more), and 194 subjects (42.9%) were treated for 1 year (at least 360 days).

7.2.2 Explorations for Dose Response

In study SRE.2674 a left/right split comparison dose-finding study, Adapalene0.1%/BP2.5% was compared to Adapalene 0.1%/BP5% in fixed combination, as well as to marketed BP formulations ranging from 2.5% to 10%. The combination product with BP2.5% was tolerated well with a similar side effect profile to both 2.5 and 5% BP alone. The combination product with BP5% induced significantly more irritation than both 5 and 10% BP alone. The lower dose combination was therefore selected for further development.

7.2.3 Special Animal and/or In Vitro Testing

The nonclinical studies performed with the fixed-combination indicate that Adapalene/Benzoyl Peroxide Gel has a similar nonclinical safety profile to that of the individual active substances. As both individual active substances were well characterized pharmacologically, and as no

interactions are likely to occur, no specific nonclinical pharmacology studies were performed with the to-be-marketed product. Safety pharmacological studies are reported for both adapalene and benzoyl peroxide and overall no impairment of major physiological body systems (including central nervous system, cardiovascular and respiratory functions) was observed.

The gelling agent, Simulgel 600 PHA, a novel excipient, was tested separately and integrally in Adapalene/Benzoyl Peroxide Gel and has not demonstrated any safety concerns.

7.2.4 Routine Clinical Testing

See section 7.4

7.2.5 Metabolic, Clearance, and Interaction Workup

For this 505(b)(2) application, the Sponsor did not perform metabolic, clearance or interaction workup, but relied on the Agency's finding for the reference listed product.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Adapalene is a widely marketed acne product and its adverse event profile is reasonably well understood. Benzoyl Peroxide has been used as an effective acne treatment for over 40 years. The common side effects for both of these products include skin irritation, dryness, redness, and peeling and are predictable. Labeling is adequate to address these safety concerns. There were no significant non-skin related adverse events felt to be related to the medication demonstrated in the development program.

7.3 Major Safety Results

7.3.1 Deaths

No deaths occurred in the clinical development program of Adapalene/Benzoyl Peroxide Gel.

7.3.2 Nonfatal Serious Adverse Events

All SAEs were unrelated to study medication.

One SAE was reported in Study SRE.2683 (hospitalization due to pneumothorax).

In the two well-controlled studies SRE.18094 and SRE.18087 a total of six (6) subjects experienced a total of 7 SAEs. Three subjects continued in the studies after reporting the SAEs

of worsening of depression (Adapalene/Benzoyl Peroxide Gel), mood disorder (Adapalene Gel), left hip abscess with cellulitis caused by staphylococcal infection (these two AEs were experienced by an Adapalene Gel treated subject). Two subjects treated with Adapalene/Benzoyl Peroxide Gel discontinued the studies for the events of drug abuse and a suicide attempt. One subject had a miscarriage which occurred after the study was completed. (Gel Vehicle).

Table 19 Subjects with Serious Adverse Events in SRE.18094 and SRE, 18087

Source: SRE.18094, Section 14.3, Table SAF 6.2; SRE.18087, Section 14.3, Table SAF 6.2 (pg. 46 Summary of Clinical Safety)

Treatment	Subject	AE Diagnosis	Preferred Term (MedDRA v6.1)	D/C	Severity	Relation to Study Drug
Study 18094						
Adapalene/BPO	143	Substance abuse	Drug Abuser	**Yes**	Severe	**Definitely unrelated**
Study 18087						
Adapalene/BPO	91206	Worsening of depression	Depression	No	Moderate	Unlikely
	92098	Attempted suicide	Suicide Attempt	**Yes**	Severe	**Unlikely**
Adapalene	90715	Left hip abscess	Abscess	No	Moderate	Unlikely
		Cellulitis-methicillin resistant staphylococcus aureus	Cellulitis Staphylococcal	No	Moderate	Unlikely
	91855	Hospitalization for mood disorder	Affective Disorder	No	Severe	Unlikely
Vehicle	90965	Miscarriage	Abortion Spontaneous	No	Severe	Unlikely

In the 1-year open-label study (SRE.18089) five subjects experienced a total of 6 SAEs all unrelated to study medication. These included depression, staphylococcal infection, clavicle fracture, syncope, bipolar disorder, and drug abuser. The two SAEs of bipolar disorder and drug abuser were experienced by the same subject. The SAE of staphylococcal infection was on the lower leg (a non-treated area) after an episode of trauma.

Table 20 Subjects with Serious Adverse Events in SRE.18089

Treatment	Subject	AE Diagnosis	Preferred Term (MedDRA v6.1)	D/C	Severity	Relation to Study Drug
Adapalene/BPO	053	syncope episode cause unknown	Syncope	No	Severe	Unlikely
	303	staph infection left lower leg due to delayed trauma intervention	Staphylococcal Infection	No	Severe	Unlikely
	310	bipolar disorder	Bipolar Disorder	No	Severe	Unlikely
		substance abuse	Drug Abuser	No	Severe	Unlikely
	342	non-healing fracture of right clavicle	Clavicle Fracture	No	Moderate	Definitely unrelated
	410	hospitalization for acute depression	Depression	No	Moderate	Definitely unrelated

Source: Sponsor's Summary of Clinical Safety, Section 2.7.4

In the ongoing study, SPR.18088, 6 subjects experienced eight (8) SAEs. Three SAEs were exacerbations of one subject's pre-existing condition (schizoaffective disorder) that led to hospitalization and discontinuation from the study. The remaining five (5) SAEs were a furuncle, a bike accident leading to C2 vertebrae fracture, an aggravation of pre-existing scoliosis, acute appendicitis and an abscess on a finger. In the ongoing study SPR.29058, two SAEs have so far occurred, depression with suicidal thoughts and concussion following a bicycle accident.

7.3.3 Dropouts and/or Discontinuations

Most of the Adverse Events leading to discontinuation were caused by the well known irritative properties of adapalene and benzoyl peroxide.

In Study SRE.2674 seven subjects (7 of 60, 11.7%) discontinued the study due to a related Adverse Event of irritant dermatitis (related to Adapalene 0.1%/Benzoyl Peroxide 2.5% for two subjects, related to Adapalene 0.1%/Benzoyl Peroxide 5% for four subjects, and related to Benzac AC (benzoyl peroxide) 5% gel for one subject). In study SRE.2683, 14 subjects (5.6%) had an adverse event leading to discontinuation. Of these 14 subjects, eight subjects (3.4%) had nine related AEs Leading to Discontinuation including allergic reaction (4), irritant dermatitis (4), and dermatitis (1).

In the two well controlled studies SRE.18094 and SRE.18087 a total of 24 subjects experienced AEs leading to discontinuation (12 (2.1%), 5 (0.9%), 5(0.9%), and 2 (0.4%) for Adapalene/Benzoyl Peroxide Gel, Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle, respectively).

Table 21

Adverse Events Leading to Discontinuation, SRE.18094 and SRE.18087 Combined

Treatment	Subject	AE Diagnosis	Preferred Term a	Serious	D/C	Severity	Relation to Study Drug
18094							
Adapalene/BPO	143	Substance abuse	Drug Abuser	Yes	Yes	Severe	Definitely unrelated
Adapalene	188	Impetigo on chin	Impetigo	No	Yes	Moderate	Definitely unrelated
18087							
Adapalene/BPO	90288	Severe facial itching	Pruritus	No	Yes	Severe	Probable
	90335	Peri-ocular irritation	Skin Irritation	No	Yes	Mild	Probable
	90662	Stinging/burning	Application Site Irritation	No	Yes	Severe	Probable
	90860	Rash on face (irritant dermatitis)	Dermatitis Contact	No	Yes	Moderate	Possible
	90942	Application site stinging	Application Site Irritation	No	Yes	Moderate	Probable
	91210	Facial irritation @ application site	Application Site Irritation	No	Yes	Moderate	Probable
	91362	Pustular acne flare	Acne Pustular	No	Yes	Severe	Unlikely
	91840	Contact dermatitis	Dermatitis Contact	No	Yes	Moderate	Probable
	92081	Facial stinging/burning	Application Site Irritation	No	Yes	Severe	Probable
	92098	Attempted suicide	Suicide Attempt	Yes	Yes	Severe	Unlikely

	92350	Skin irritation (face)	Skin Irritation	No	Yes	Moderate	Probable
Adapalene Gel	90333	Tooth abscess	Tooth Abscess	No	Yes	Severe	Unlikely
	91283	Rash neck-irritant contact dermatitis	Dermatitis Contact	No	Yes	Moderate	Unlikely
	92252	Irritation (facial skin)	Skin Irritation	No	Yes	Mild	Probable
	92318	Allergic dermatitis	Dermatitis Allergic	No	Yes	Moderate	Probable
Benzoyl Peroxide Gel	90327	Perioral burning	Skin Irritation	No	Yes	Mild	Possible
	90875	Irritant reaction	Skin Irritation	No	Yes	Severe	Probable
	92021	Burning	Application Site Burning	No	Yes	Mild	Probable
		Scaling	Skin Desquamation	No	Yes	Mild	Probable
		Erythema	Erythema	No	Yes	Mild	Probable
	92134	Worsening of acne	Acne	No	Yes	Moderate	Probable
	92332	Face itching	Pruritus	No	Yes	Mild	Probable
		Face swollen-mild	Swelling Face	No	Yes	Mild	Probable
Gel Vehicle	90426	Cystic-acne flare	Acne Cystic	No	Yes	Moderate	Unlikely
	92123	Irritant local contact dermatitis	Dermatitis Contact	No	Yes	Moderate	Definitely related

Source: Adapalene/Benzoyl Peroxide Gel Section 2.7.4 Summary of Clinical Safety (pg. 49)

Few systemic AEs led to discontinuation. These events included drug abuse, suicide attempt (both were in the Adapalene/Benzoyl Peroxide Gel group), and tooth abscess (Adapalene Gel).

In the 1-year long-term, open-label safety and efficacy study SRE.18089 nine subjects (of 452, 2.0%) experienced AEs leading to discontinuation. Seven (7) subjects discontinued due to dermatological AEs (contact dermatitis, cystic acne, urticaria, dry skin, acne, swelling face), one for application site irritation, and one subject due to influenza and abnormal laboratory test of increased ALT, AST, GGT, and LDH increased (the laboratory evaluations were fully reversible as confirmed by follow-up laboratory evaluations).

Table 22 Summary of Adverse Events Leading to Discontinuation, Reported by at Least 1% of Subjects, Safety Population, SRE.18089

Treatment	Subject	AE Diagnosis	Preferred Term a	Serious	D/C	Severity	Relation to Study Drug
Adapalene/BPO	117	Reaction to study drug-urticaria	Urticaria	No	Yes	Moderate	Probable
	151	Irritant contact dermatitis	Dermatitis Contact	No	Yes	Mild	Probable
	255	Worsening of acne, with cystic acne	Acne Cystic	No	Yes	Severe	Possible
	293	Worsening dryness of face	Dry Skin	No	Yes	Moderate	Definitely related
	302	Contact dermatitis of eyelids; irritant	Dermatitis Contact	No	Yes	Moderate	Probable
	388	Irritation of skin on face	Application Site Irritation	No	Yes	Moderate	Probable
	441	Nodules and cystic lesions.	Acne	No	Yes	Moderate	Definitely unrelated
	442	Flu-like symptoms treated w/ zithromax	Influenza	No	Yes	Mild	Unlikely
		(End of study early termination) abnormal lab	Laboratory Test Abnormal	No	Yes	Mild	Unlikely
	573	Swelling in face	Swelling Face	No	Yes	Moderate	Probable

Source: Sponsor's Summary of Clinical Safety, Section 2.7.4

7.3.4 Significant Adverse Events

The sponsor's product was only available in one fixed dose. Temporary adjustments to the treatment regimen were permitted as outlined in section 5.2.3 of each of the protocols for the pivotal studies (18094 and 18087) and the long term safety study (18089). If subjects experienced excessive dryness or irritation then the Investigator could consider use of an allowed moisturizer as described in section 3.5.2. If the dryness or irritation continued then an altered dosing regimen could then be considered. If the once daily dosage regimen was altered to every other day, (i.e., to treat local irritation) an attempt was to be made by the Investigator to return the subject to once daily treatment within two weeks of the interruption. This was to be documented on the Case Report Form. The protocols did not allow any other topical medication treatment, other than the study drug, permitted on the face.

7.3.5 Submission Specific Primary Safety Concerns

There were no additional submission specific primary safety concerns

7.4 Supportive Safety Results

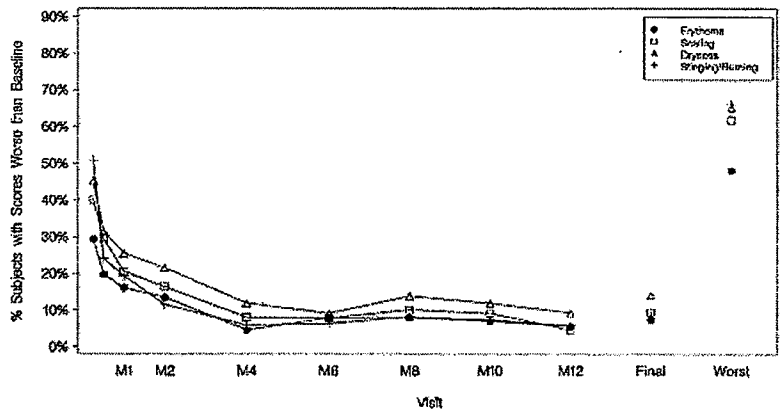
7.4.1 Common Adverse Events

For both pivotal studies (18094 and 18087) and for the long term safety study (18089) the local tolerability of the study medications was assessed by the investigator by evaluating erythema, scaling, dryness and stinging/burning on a 4-point scale of "0" (none) to "3" (severe). Local Tolerability was evaluated at baseline and at each post-baseline visit. Erythema, scaling and dryness were evaluated by the investigator, while stinging/burning was recorded by the investigator after discussion with the subject.

For both pivotal studies (18094 and 18087) and for the long term safety study (18089) signs and symptoms of local tolerability were recorded as adverse events, if the severity of the event caused interruption or discontinuation of the study medication, or the subject required concomitant medication. Any additional sign or symptom not captured by the four signs and symptoms (erythema, scaling, dryness, and stinging/burning) were to be recorded as an AE.

The incidence of the signs and symptoms of local tolerability worse than Baseline were highest at Week 1 of treatment and subsided thereafter in both the pivotal studies and in the long term safety study. The time course of signs and symptoms of local tolerability are demonstrated in the following figure from the sponsor's Summary of Clinical Safety (pg. 42).

Figure 5 **Time course of Signs and Symptoms of Local Tolerability, SRE.18089**



Final: The last available data observed during the post-baseline period.
Worst: The data observed with the highest severity during the post-baseline period.
M: Month
Data source: SRE.18089, Section 14.3, Figure SAF 1

Most of the signs and symptoms of local tolerability were mild or moderate in severity. The following table from the Summary of Clinical Safety (pg. 35) shows the findings for the combined pivotal studies.

	Adapalene/ Benzoyl Peroxide Gel Na = 553* n (%)	Adapalene Gel N a = 562* n (%)	Benzoyl Peroxide Gel N a = 557* n (%)	Gel Vehicle N a = 481* n (%)
Erythema	**225 (40.7)**	**174 (31.0)**	**104 (18.7)**	**97 (20.2)**
1 = mild	148 (26.8)	121 (21.5)	73 (13.1)	72 (15.0)
2 = moderate	72 (13.0)	51 (9.1)	30 (5.4)	24 (5.0)
3 = severe	5 (0.9)	2 (0.4)	1 (0.2)	1 (0.2)
Scaling	**253 (45.8)**	**211 (37.5)**	**100 (18.0)**	**88 (18.3)**
1 = mild	192 (34.7)	175 (31.1)	89 (16.0)	84 (17.5)
2 = moderate	58 (10.5)	35 (6.2)	11 (2.0)	4 (0.8)
3 = severe	3 (0.5)	1 (0.2)	0 (0.0)	0 (0.0)
Dryness	**302 (54.6)**	**244 (43.4)**	**135 (24.2)**	**87 (18.1)**
1 = mild	224 (40.5)	202 (35.9)	121 (21.7)	80 (16.6)
2 = moderate	74 (13.4)	39 (6.9)	14 (2.5)	7 (1.5)
3 = severe	4 (0.7)	3 (0.5)	0 (0.0)	0 (0.0)
Stinging/Burning	**328 (59.3)**	**178 (31.7)**	**79 (14.2)**	**53 (11.0)**
1 = mild	225 (40.7)	139 (24.7)	72 (12.9)	45 (9.4)
2 = moderate	84 (15.2)	31 (5.5)	5 (0.9)	8 (1.7)
3 = severe	19 (3.4)	8 (1.4)	2 (0.4)	0 (0.0)

In the long term safety study 18089, few subjects experienced severe signs and symptoms of local tolerability . The exact figures are 3 (0.7%), 2 (0.4%), 5 (1.1%) and 15 (3.3%) of the subjects for severe erythema, scaling, dryness, and stinging/burning, respectively).

The majority of the time moisturizers and temporary adjustments to the treatment regimen managed these events. Overall, the tolerability profile observed in each subpopulation (gender, race, and age) was consistent with that observed for the total population.

In looking at all adverse events in the pivotal studies combined, the incidence was comparable between Adapalene/Benzoyl Peroxide Gel and Adapalene Gel but slightly higher compared to Benzoyl Peroxide Gel and Gel Vehicle. The number of subjects with AEs was comparable among the groups (35.3%, 37.3%, 28.2%, and 27.8% for Adapalene/Benzoyl Peroxide Gel, Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle, respectively).
Unrelated adverse events (as categorized by the sponsor using MEDRA classification) with an incidence of at least 1% expected to occur in the population treated were reported with similar

incidences in all four treatment groups in the System Organ Classes of "Infections and Infestations", "Respiratory, Thoracic, and Mediastinal Disorders", "Gastrointestinal Disorders", and "Nervous System Disorders" in studies 18094 and 18087 combined as shown in table 17 from ISS (pg.45).

Table 17 Most Frequent Adverse Events, Reported by at Least 1% in Any Group by System Organ Class and Preferred Term SRE.18094 and SRE.18087 Combined

System Organ Class / Preferred Terma	Adapalene/ BPO N = 564	Adapalene Gel N = 568	BPO Gel N =564	Gel Vehicle N = 489
Total Number of AE(s)	**316**	**337**	**243**	**188**
Total Number (%) of Subjects with AE(s)	**199 (35.3%)**	**212 (37.3%)**	**159 (28.2%)**	**136 (27.8%)**
Skin and Subcutaneous Tissue Disorders	**83 (14.7%)**	**72 (12.7%)**	**38 (6.7 %)**	**28 (5.7%)**
Dry Skin	42 (7.4%)	36 (6.3%)	12 (2.1%)	14 (2.9%)
Contact Dermatitis	18 (3.2%)	20 (3.5%)	4 (0.7%)	3 (0.6%)
Pruritus	7 (1.2%)	5 (0.9%)	13 (2.3%)	4 (0.8%)
Skin Irritation	7 (1.2%)	2 (0.4%)	4 (0.7%)	0
Infections and Infestations	**68 (12.1%)**	**89 (15.7%)**	**76 (13.5%)**	**68 (13.9%)**
Nasopharyngitis	20 (3.5%)	33 (5.8%)	28 (5.0%)	22 (4.5%)
Upper Respiratory Tract Infection	11 (2.0%)	14 (2.5%)	17 (3.0%)	19 (3.9%)
Sinusitis	7 (1.2%)	7 (1.2%)	4 (0.7%)	4 (0.8%)
Gastroenteritis Viral	3 (0.5%)	6 (1.1%)	3 (0.5%)	1 (0.2%)
General Disorders and Administration Site Conditions	**30 (5.3%)**	**16 (2.8%)**	**7 (1.2%)**	**7 (1.4%)**
Application Site Burning	15 (2.7%)	4 (0.7%)	2 (0.4%)	2 (0.4%)
Application Site Irritation	8 (1.4%)	6 (1.1%)	2 (0.4%)	1 (0.2 %)
Injury, Poisoning and Procedural Complications	**27 (4.8%)**	**26 (4.6%)**	**16 (2.8%)**	**9 (1.8%)**
Sunburn	7 (1.2%)	9 (1.6%)	3 (0.5%)	5 (1.0%)
Respiratory, Thoracic and Mediastinal Disorders	**24 (4.3%)**	**23 (4.0%)**	**14 (2.5%)**	**20 (4.1%)**
Pharyngolaryngeal Pain	7 (1.2%)	6 (1.1%)	7 (1.2%)	5 (1.0%)
Nasal Congestion	6 (1.1%)	3 (0.5%)	3 (0.5%)	3 (0.6%)
Cough	4 (0.7%)	3 (0.5%)	3 (0.5%)	7 (1.4%)
Gastrointestinal Disorders	**10 (1.8%)**	**12 (2.1%)**	**11 (2.0%)**	**11 (2.2%)**
Nausea	1 (0.2%)	6 (1.1 %)	4 (0.7%)	1 (0.2%)
Nervous System Disorders	**10 (1.8%)**	**18 (3.2%)**	**11 (2.0%)**	**8 (1.6%)**
Headache	9 (1.6%)	16 (2.8%)	7 (1.2%)	7 (1.4%)

a:Multiple occurrences within a System Organ Class (SOC) by a subject were counted once per SOC.

a:Multiple occurrences of a Preferred Term by a subject were counted once per Preferred Term.

@: A subject was counted once even if the subject experienced more than one AE during the study.

The sponsor identified the "Skin and Subcutaneous Tissue Disorders" class with preferred terms of dry skin, contact dermatitis, pruritis, skin irritation, and the "General Disorders and Administration Site Conditions" with the preferred terms: application site burning and application site irritation, to be the two most relevant classes of AEs for a fixed combination of components with well-known irritative properties.

In the class "Skin and Subcutaneous Tissue Disorders" the frequencies for AEs were 14.7%, 12.7%, 6.7%, and 5.7% for Adapalene/Benzoyl Peroxide Gel, Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle, respectively and in "General Disorders and Administration Site Conditions" the frequencies for AEs were 5.3%, 2.8%, 1.2%, and 1.4% for Adapalene/Benzoyl Peroxide Gel, Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle, respectively (Table 17)

7.4.2 Laboratory Findings

In Study SRE.18097 routine blood chemistry, hematology, and urinalysis were performed at Screening and Day 30 and in the open-label Long-Term Safety Study SRE.18089 at Screening, Month 6, and Month 12. No clinically relevant drug-related changes in blood chemistry, hematology, or urinalysis were observed following therapy with Adapalene/Benzoyl Peroxide Gel. Further, there were no clinically relevant changes in median laboratory values from Screening to Month 6 or to Month 12 in SRE.18089. No routine laboratory tests were performed in the well-controlled studies SRE.18094 and SRE.18087.

7.4.3 Vital Signs

In SRE.18087, vital signs were measured. No clinically relevant drug related changes were observed in vital signs with Adapalene/Benzoyl Peroxide Gel.

7.4.4 Electrocardiograms (ECGs)

No electrocardiogram data was collected during any phase of drug development. The sponsor submitted the following rationale (in addendum dated 06/06/08) for why a thorough QT/QTc study is not needed with EPIDUO:

> Adapalene/Benzoyl Peroxide Gel is the fixed combination of the two well characterized active ingredients at their lowest approved concentrations with an intended once daily therapeutic regimen. This combination product has been developed in the same indication, same population and the same route of administration as the individual ingredients already approved.

In study SRE 18097, two of twelve subjects (9 (2%) of 386 plasma samples) and three of twelve subjects (12 (3%) of 375 plasma samples) treated with Adapalene/Benzoyl Peroxide Gel and the Adapalene 0.1 Gel Monad, respectively, had quantifiable (LOQ: 0.1ng/ml) systemic exposure to adapalene. The highest exposure (Cmax) observed in this study was 0.13 ng/ml and 0.16 ng/ml for Adapalene/Benzoyl Peroxide Gel and the Adapalene 0.1% Gel Monad, respectively. Consequently, systemic exposure to adapalene from both the Adapalene/Benzoyl Peroxide Gel and the Adapalene 0.1% Gel Monad applied under conditions of maximized use was consistently low. The Benzoyl Peroxide Monad of the fixed combination did not increase the systemic exposure to adapalene.

Systemic exposure to benzoyl peroxide was not evaluated by the Applicant. Topical benzoyl peroxide is rapidly metabolized to benzoic acid in the skin (S. Nacht et al., J Am Acad. Dermatol 4:31-37, 1981). Benzoic acid is an endogenous compound; it is also widely used as a food additive. The absorbed quantity of benzoic acid after topical application of Adapalene/Benzoyl Peroxide under maximized conditions of use (i.e. 2g/day) is less than 10% of the Acceptable Daily Intake established by the World Health Organization (NDA Section 2.6.6. Toxicology Written Summary -Benzoyl peroxide).

There were no findings indicative of cardiotoxic effects in the pre-clinical studies with Adapalene/Benzoyl Peroxide or the monads (adapalene and benzoyl peroxide).

Since the launch of these products and until 31 March 2008, there were no cases of arrhythmia or other ECG changes (including any changes in ventricular repolarization) reported in the Galderma Pharmacovigilance database.

With more than ____ patients exposed to adapalene and ____ patients exposed to benzoyl peroxide, the Galderma post-marketing surveillance data support the favorable safety profile of each individual active substance. In particular, there was no signal of any effect on cardiac repolarization. b(4)

No reports of cardiotoxicity with either adapalene or benzoyl peroxide are documented in the literature.

Based upon the low systemic availability combined with the long history of marketed use of both individual components of EPIDUO, as well as the lack of a cardiovascular signal with oral retinoids and oral benzoic acid this reviewer feels that the systemic safety of the fixed combination product is unlikely to differ from the approved and marketed adapalene and benzoyl peroxide products.

Based on the lack of pre-clinical or clinical findings indicative of cardiotoxic effects of adapalene or benzoyl peroxide either as monotherapy or in fixed-combination I agree with the applicant that there is no need to perform a thorough QT/QTc study.

7.4.5 Special Safety Studies

Dermal Safety Study Results

A total of 4 special safety studies were performed with the to be marketed formulation. These included study SRE.2687 the cumulative irritation study, study SRE.2683 the cutaneous sensitization study, study SRE.2681 the phototoxicity study and study SRE.2682 the photoallergenicity study.

Study SRE.2687

The aim of this study was to assess the cumulative irritancy potential of a combination product with adapalene 0.1 % plus benzoyl peroxide 2.5% in a gel after repeated applications to the skin of healthy subjects in comparison with adapalene gel 0.1 %, benzoyl peroxide gel 2.5 % and 10%, and tazarotene gel 0. 1%.

The study was a single-center, active-controlled, single-blind (Investigator/Evaluator-masked), intra-individual comparison with randomized applications, in twenty-five (25) consenting healthy subjects (10 males and 15 females), aged from 20 to 78 years (mean age = 47.3), meeting specific inclusion/exclusion criteria. The subjects received one patch every week day of each of the products (for a total of 15 applications). Products were applied five times a week (every day except weekends) for 3 weeks (under semi-occlusive conditions ie: protective system avoiding clothes rubbing consisting of a compress covered with an adhesive dressing ——— on the upper back). Skin reactions were evaluated before each product application. The study lasted 21 days. b(4)

Twenty-five subjects were randomized; one subject was withdrawn on Day 1 because of a protocol violation (non-compliance with washout period relative to participation in another study). Twenty-four subjects completed the study as planned.

The schedule of assessments below (from the Clinical study report No: RD.03.SRE.2687, page 19) details the evaluations carried out at each visit.

STUDY FLOW CHART					
Parameters	**Screening[1]**				
Informed Consent	X				
Inclusion/Exclusion Criteria	X				
Demographics	X				
Previous Therapy	X				
Medical History	X				
1st WEEK					
	Inclusion/ Day 0 Monday	**Day 1** Tuesday	**Day 2** Wednesday	**Day 3** Thursday	**Day 4** Friday
Inclusion/exclusion criteria	X				
Skin assessment	X	X	X	X	X
On-site Dose Application	X	X	X	X	X
Adverse Events	X	X	X	X	X
Concomitant Medications	X	X	X	X	X
2nd WEEK					
	Day 7 Monday	**Day 8** Tuesday	**Day 9** Wednesday	**Day 10** Thursday	**Day 11** Friday
Skin assessment	X	X	X	X	X
On-site Dose Application	X	X	X	X	X
Adverse Events	X	X	X	X	X
Concomitant Medications	X	X	X	X	X
3rd WEEK					
	Day 14 Monday	**Day 15** Tuesday	**Day 16** Wednesday	**Day 17** Thursday	**Day 18** Friday
Skin assessment	X	X	X	X	X
On-site Dose Application	X	X	X	X	X
Adverse Events	X	X	X	X	X
Concomitant Medications	X	X	X	X	X
4th WEEK					
	Day 21 Monday				
Skin assessment	X	[1] Must be within 14 days prior to Day 0 [2] Was only to be performed on Day 21 or earlier in case of study discontinuation			
Adverse Events	X				
Concomitant Medications	X				
Exit Form	X[2]				

al version dated: 12 November 2002 PAGE 19

Subjects were to be seen daily Monday to Friday for three weeks. At each daily visit, skin assessment to check for the presence of erythema, edema and other local reactions was performed on each application zone prior to the next application.

ERYTHEMA

The response was to be scored after removal of each semi-occlusive patch. The following grading scale was used for erythema:

SCORE	DEFINITION	DESCRIPTION
0	No reaction	No erythema
0.5	Erythema barely visible	Erythema barely visible
1	Mild erythema	Slight pinkness present
2	Moderate erythema	Definite redness easily recognized
3	Severe erythema	Intense redness

from the Clinical study report No: RD.03.SRE.2687, page 29

EDEMA

At each evaluation, edema was assessed according to the following scale:

SCORE	DEFINITION	DESCRIPTION
0	None	No induration
1	Mild edema	Slight tenseness of the skin
2	Moderate edema	Moderate thickening of the skin with edematous feel
3	Severe edema	Firm resistance to distortion, non-distensible

from the Clinical study report No: RD.03.SRE.2687, page 29

In case of severe irritation (judged by the investigator on the basis of the clinical evaluation and the symptoms described by the subject) on any zone, application of the product was to be discontinued on the incriminated site(s), which was no longer to be scored by the investigator.

For each subject and each product a Cumulative Irritancy Index (CII) was to be computed as the sum of all erythema scores across readings (Day 1 to Day 21) divided by the number of readings. If an application was discontinued due to a severe reaction on a zone (erythema=3), this score was to be carried forward for the zone in question from the day following the last application until the end of the study. A Mean Cumulative Irritancy Index (MCII) was to be calculated for each product by averaging individual CIIs across subjects. Individual CIIs were to be submitted to analysis of variance for Latin square design, with effects for subject, zone and product, followed by the Tukey multiple comparison test comparing all products, at the 5% significance level.

Worst score for edema

The worst score for edema was to have been summarized in frequency table for each product. However, since there were very few occurrences of edema, whereas erythema was more frequent, the worst erythema score was calculated instead.

Results:

Worst erythema score by product

- Worst erythema score N (%)	0	0.5	1	2	3
Adapalene 0.1%	16 (66.67)	7 (29.17)	1 (4.17)	0	0
Benzoyl peroxide 10%	20 (83.33)	2 (8.33)	2 (8.33)	0	0
Benzoyl peroxide 2.5%	17 (70.83)	4 (16.67)	2 (8.33)	1 (4.17)	0
Combination	16 (66.67)	4 (16.67)	3 (12.50)	1 (4.17)	0
Tazarotene 0.1%	1 (4.17)	2 (8.33)	5 (20.83)	8 (33.33)	8 (33.33)
Vehicle	18 (75.00)	5 (20.83)	1 (4.17)	0	0

from the Clinical study report No: RD.03.SRE.2687, page 47

Most of the subjects showed no erythema (66 to 83% of subjects depending on the product) except for tazarotene where only 4% of subjects were scored 0. Indeed, tazarotene was much more irritating: it was the only product leading to grade 3 erythema reactions.

The MCII for each product is given in table 6 section 14 of the Clinical study report No: RD.03.SRE.2687 presented below.

Test products	MCII (mean ± SD)
Adapalene 0.1%	0.017 ± 0.028
Benzoyl peroxide 10%	0.026 ± 0.081
Benzoyl peroxide 2.5%	0.043 ± 0.107
Combo/benzoyl peroxide 2.5%	0.046 ± 0.120
Tazarotene 0.1%	0.616 ± 0.409
Vehicle	0.011 ± 0.021

The cumulative irritation observed with Adapalene/Benzoyl Peroxide Gel when applied for 21 days under semi-occlusion to the backs of 25 healthy subjects was significantly less than the irritation observed with the retinoid tazarotene 0.1% gel. The cumulative irritation was not significantly different from marketed benzoyl peroxide products Benzac 10% gel or the monad (Benzoyl Peroxide 2.5% Gel).

Study SRE.2683

The aim of this study was to assess the cutaneous contact sensitization potential of a combination product with adapalene 0.1 % plus benzoyl peroxide 2.5% in a gel after repeated applications to the skin of healthy subjects compared to adapalene 0.1 % alone, BPO 2.5% alone, vehicle and white petrolatum (negative control).

This study was conducted as a single center, vehicle and placebo controlled, randomized, single blind (investigator/evaluator masked), intra-individual comparison with randomized applications in 251 healthy Subjects (56 males and 195 females) aged between 18 and 65 (mean age:41years). There were 24 patients who discontinued the study, 14 due to adverse events, 6 due to subject request, 2 due to protocol violations, one lost to follow –up and one "other". There were 227 subjects who participated in the challenge phase and completed the study.

This study was divided into three phases:

- An induction phase during which the products were applied under occlusive conditions, to the upper back, three times a week (e.g., Monday, Wednesday, Friday), for 3 weeks. Each patch was removed after 48 hours or 72 hours (e.g., from Friday to Monday). Skin reactions were assessed 15 to 30 minutes after removal of the patches. The following grading scale was used:

  0 No erythema
  0.5 Equivocal erythema
  1 Slight erythema with slight edema (more palpable than visible)
  2 Moderate erythema with or without papules
  3 Severe erythema with papules
  4 Severe erythema and edema with reaction spreading beyond the tested area

  Any of the following signs; blister, crust, superficial erosion, oozing, vesicles, or a grade 4 irritation would entail a change of patch site.

- A two-week rest period without product application.

- A challenge phase during which the products were applied once to naive sites to the lower back and were removed after 48 hours. Each of the 251 subjects received all test materials (intra-individual comparison). Skin reactions were scored 15 to 30 minutes after removal of the patches and then 48 and 72 hours later. If an equivocal reaction occurred, a 96 hour assessment had to be performed. The following grading scale was used:

  0 Negative reaction

0.5 Doubtful reaction: mild redness only
1 Weak positive reaction: red and slightly thickened skin (small papules)
2 Strong positive reaction: red, swollen skin with individual vesicles
3 Extreme positive reaction: intense redness and swelling with coalesced large blisters or spreading action beyond the tested area.

At the end of the challenge phase, the Investigator had to give her opinion concerning a possible sensitization reaction, by evaluation of each site using the following categories:

Diagnostic Scale:

0 Negative
1 Equivocal
2 Positive

Results:

During induction, due to severe irritation, 230 patch applications were stopped in 118 subjects (additionally, 3 subjects were discontinued during Week 1 due to irritation).

- 113 patches with the combination product
- 108 patches with BPO 2.5%
- 5 patches with adapalene 0. 1 %
- 4 patches with vehicle
- None with white petrolatum

As these applications were mainly stopped at the end of the induction phase, due to severe irritation, which is known to increase penetration of the product, these interruptions were not expected to change the results of the study.

During the challenge phase, sensitization reactions (defined as a score 2 in the diagnosis scale-at least red swollen skin with vesicles) were reported in 146 subjects out of the 227 who completed the study as follows:

144 subjects (63.4%) with the combination product
142 subjects (62.6%) with monad benzoyl peroxide 2.5% gel
23 subjects (10.1%) with Gel Vehicle
21 subjects (9.3%) monad adapalene 0.1% gel
4 subjects (1.8%) with white petrolatum

Severe irritation reactions, with clinical signs similar to those of allergy were observed during both induction and challenge making interpretation difficult. Therefore, all the subjects with

equivocal or positive sensitization reactions were offered rechallenge to try to clarify if some of these reactions were false positives. Since irritation is concentration dependent, dilutions (of the combination product) and lower concentrations (of the BPO) were used. Adapalene 0.1% was tested in white petrolatum and five ingredients in the vehicle were added to the panel. The results of the rechallenge performed in the 66 willing subjects (out of 174 subjects who were offered rechallenge) are below as reported in a table from page 43 of the protocol for study 2683.

Products	Negative (0)	Equivocal (1)	Positive (2)
Combination product 1/4th	15	1	50
Combination product 1/8th	11	4*	51**
BPO 1%	16	1	49
Adapalene gel 0.1%	65	1	0
Vehicle	51	8	7
Disodic EDTA	66	0	0
Propylene glycol 5	65	0	1
Simulgel 600	62	4	0
White petrolatum	66	0	0

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* Of these 4 subjects, 3 had negative reactions (score 0) to Combination product 1/4th.
** One subject (n°121) had negative reactions (score 0) to Combination product 1/4th

These results confirmed that 50 of the 55 consenting subjects originally suspected of sensitivity to the combination product were indeed confirmed to be sensitive. Similarly 49 of the 55 tested subjects suspected to be sensitive to BPO 2.5% were confirmed.

The extremely high number of sensitizations to the combination product and to benzoyl peroxide 2.5% observed in Study SRE.2683 + Amendment 01 + Amendment 02 is unexplained. The sponsor proposes several suggested contributors to the unusually high rate of sensitization seen. During challenge, severe irritation reactions occurred at the benzoyl peroxide treated sites (the monad Benzoyl Peroxide 2.5% Gel and the fixed-combination Adapalene/Benzoyl Peroxide Gel) interfering with the evaluation of the reactions.

Irritation was initially not to be analyzed. However, a possible link between irritation and sensitization was suspected and an additional statistical analysis was carried out to compare irritation observed during induction (worst score of erythema) with sensitization observed during challenge. The subjects were classified into 4 categories based on the worst score of erythema observed during induction:

- Subjects with a skin reaction scored inferior or equal to 1 (no erythema to slight erythema),
- Subjects with a skin reaction equal to 2 (moderate erythema with or without papules)
- Subjects with a skin reaction equal to 3 (severe erythema with papules)
- Subjects with a skin reaction equal to 4 (severe erythema and edema with reaction spreading beyond the tested area)

The sensitization rate was then calculated in each group. Results showed that there was a close correlation between irritation (during induction) and sensitization (during challenge). In the group of subjects with a worst score inferior or equal to 1 (N=11), the sensitization rate to the combination product was 8.3%. In contrast, in the group of subjects with a worst score of 4, the

sensitization rate to the combination product was 96.7%. (See the table below). The same correlation was observed with the subjects sensitized to BPO 2.5%.

The sponsor stated that this confirmed that when little or no irritation was reported during induction the level of sensitization was close to that reported in acne patients after treatment with marketed benzoyl peroxide products under normal conditions of use. The table below is from CLINICAL STUDY REPORT RD.03.SRE.2683 page 44.

The results of the additional statistical analysis:

	Induction	Challenge			
	Worst Score for Erythema (irritation)	SENSITIZATION REACTIONS			
		0		2	
Combination product					
		N	%	N	%
	≤ 1	11	91.67	1	8.33
	2	56	66.67	28	33.33
	3	15	14.85	86	85.15
	4	1	3.33	29	96.67
	All	83	36.56	144	63.44
BPO 2.5%					
	≤ 1	24	92.31	2	7.69
	2	47	58.02	34	41.98
	3	12	12.90	81	87.10
	4	2	7.41	25	92.59
	All	85	37.44	142	62.56

In an attempt to put this rate of sensitization into perspective a literature search of published rates of allergy to benzoyl peroxide was performed. In an article "Benzoyl Peroxide Carcigenicity and Allergenicity by Daniel Hogan, MD published in The International Journal of Dermatology in 1991 the author states

> The reported incidence of positive patch test reactions (to BPO) varies from 0% to 76%. The highest reported incidence was in a group of 41 patients with leg ulcers treated with 20% benzoyl peroxide under occlusion. In the same article Hogan summarizes the results of multiple studies in the following table

Table 1. Frequency of Positive Patch Test Reactions to Benzoyl Peroxide Among Patients Using Benzoyl Peroxide and Controls

Author (year)	*Diagnosis of Patients*	*No. of Patients*	*Vehicle for Patch Tests*	*Positive Reactions (M/F)*			
				5% BP	*2% BP*	*1% BP*	*0.1% BP*
Eaglstein (1968)	Miscellaneous	41	Petrolatum	2.4%	—	—	—
Jensen (1980)	Leg ulcer treated with 10% BP gel	16	Petrolatum	—	50%	—	—
Lindemayr (1981)	Miscellaneous	94	Gel	3.1% (3%/4%)	—	—	—
	Contact dermatitis	69		5.8% (11%/2%)	—	—	—
	Acne treated with BP	59		5%	—	—	—
Rietschel (1982)	Acne controls	32	BP gel in petrolatum	—	—	19%	—
	BP × 12 wk for acne	28		—	—	25%	4%
Haustein (1985)	Acne before BP	100	Petrolatum	19% (12%/29%)	—	2% (0%/5%)	0%
	Acne after 8 wk BP	93		34% (28%/43%)	—	0%	0%
	Acne on long-term BP	72		29% (27%/33%)	—	0%	0%
	Controls	100		29% (29%/29%)	—	0%	0%
Balato (1984)	Acne	50	Petrolatum	0%	0%	—	—
Agathos (1984)	Acne	13	Petrolatum	—	0%	0%	—
	Dermatitis	739		—	—	4.1%	—
	Leg ulcer treated with 20% BP lotion	41		—	—	76%	—

BP: benzoyl peroxide.

In "Experimental Contact Sensitization with Benzoyl Peroxide" by Richard Poole et al published in Archives of Dermatology in 1970 (vol 102, pg 400-404) the author found a 40% sensitization rate to benzoyl peroxide 10% and sulfur 1% in ointment. Rechallenge 2 months later "clearly established that it was the benzoyl peroxide that was the sensitizing agent." The product was tested using the "repeated insult patch test" conditions which consisted of nine 24 hour applications under occlusion to the upper arm over a three week period followed by a 2 week resting period and then a single 24 hour challenge.

In "Contact Sensitization to Benzoyl Peroxide" by James Leyden et al published in Contact Dermatitis in 1977 (vol 3, pg 273-275) the author found a 76% sensitization rate using four different formulations of BP (two 5% and two 10% gels) when tested under maximized conditions (applied under occlusion to the same site for five 48 hour periods followed 10-14 days later with a 48 hour patch test).

With regard to the reactions seen to the adapalene, vehicle and even to petrolatum in 4 subjects, the sponsor proposed additional possible explanations. Seventeen out of eighteen subjects with suspected allergy to vehicle and adapalene were also positive to the combination product and to BPO 2.5% consequently, an "angry back syndrome" was suspected. "Angry back syndrome", also know as "excited skin syndrome" is defined in Fisher's "Contact Dermatitis" as "a regional phenomenon caused by the presence of a strongly positive reaction, a state of skin hyperreactivity in which other patch-test sites become reactive, especially to marginal irritants". Rechallenge with individual suspected allergens separated physically on the body and applied to "naïve" sites after a period of no exposure is recommended to clarify the situation.

None of the patients initially reported as sensitive to adapalene 0.1% reacted to that product in petrolatum upon rechallenge and may indeed represent "false positives". The lack of

hypersensitivity seen to this product in the clinical trials and in marketed use supports this assumption.

Surprisingly 7 of the 9 consenting patients who reacted to the vehicle were confirmed to be sensitive though in only one case was the culprit (propylene glycol) specifically identified. In addition, there were 4 equivocal reactions to the simulgel, a novel excipient. The gelling agent, Simulgel 600 PHA, was tested separately in studies HICV 97.271 (assessment of acute irritation potential), HICV 97.270 (assessment of acute irritation potential), le 491/98.4213 (assessment of cutaneous tolerance after repeated administration) and If 037/99.0238 (assessment of cutaneous tolerance and sensitization potential) and integrally in Adapalene/Benzoyl Peroxide Gel and no irritancy or sensitization signal has been detected.

Events of suspected sensitization were few (and none could be confirmed) in the well–controlled studies (SRE.18094 and SRE.18087) and the long-term study (SRE.18089).

In conclusion, the same incidence of sensitization was found for Adapalene/Benzoyl Peroxide Gel and Benzoyl Peroxide 2.5% Gel, the presence of adapalene in the fixed-combination did not increase the sensitization potential of benzoyl peroxide alone. The occlusive conditions of the testing seem to have resulted in an unusually high rate of sensitization to both BP 2.5% alone and to the combination product (most likely due to the presence of BP 2.5% as a component of that combination product). This is in contrast to the lack of a signal in the irritancy study where semi-occlusive conditions were used. It is also in marked contrast to the lack of a signal in the clinical trials. These findings are not dissimilar from what was found in a literature search of provocative testing with benzoyl peroxide under occlusive conditions. This will need to be addressed in labeling.

Study SRE.2681

Study SRE.2681 compared the phototoxic potential of the Adapalene/Benzoyl Peroxide Gel, the monads, Adapalene 0.1% Gel, Benzoyl Peroxide 2.5% Gel, and Gel Vehicle in 25 healthy white caucasian subjects (13 females and 12 males), aged from 22 to 55 years (mean age = 34 years) with skin phototype II (N=1) and III (N=24).

The MED (Minimal Erythema Dose) of UVA/UVB was determined for each subject between Day 1 and Day 2. At Day 1, test products were applied (50 uL) to two sets of 4 patch sites (a fifth site remained untreated) under occlusive conditions for 24 hours. At Day 2, after removal of the patches, one set of 5 patch sites was irradiated with 20 J/cm2 of UV A. Following irradiation with UVA, the irradiated sites were further exposed to 0.8 MED of UVA/UVB light. The other set of 5 patch sites served as non-irradiated control. All patch sites were evaluated 60 min after irradiation, and then 24h (Day 3), 48h (Day 4) and 72lh(Day 5) after the irradiation procedure.

All 25 subjects were evaluable for phototoxicity and safety.

The mean MED measured on the 25 subjects was 130 +/- 45 MED/min x sec (45.5 mJ/cm2). The mean erythema score observed at Day 3 (24 hours after irradiation and patch removal) was higher for the irradiated site as compared to the non irradiated site for the untreated zone (control). A similar difference between irradiated and non-irradiated sites was also observed for the tested products. In this study, the combination product and BPO 2.5% alone showed a similar high irritant profile whereas adapalene 0.1 % gel and vehicle were well tolerated. These local reactions interfered with the clinical assessment of phototoxicity and led to the repatch of eight (8) subjects out of 25.

In accordance with the protocol, patch tests were conducted in all these subjects to confirm either allergy or irritation. Following these patch-test sessions, allergic reactions to BPO were confirmed in 4 subjects. These sensitizations were not initiated by the tested product. The onset of an active sensitization following the first application of a product takes a minimum of ten days and the reactions observed during this study appeared within 48 hours. The application of a patch containing BPO revealed a previously undetected sensitization to this product in these four subjects. The phototoxic potential of Adapalene/Benzoyl Peroxide Gel was not increased compared to Benzoyl Peroxide 2.5% Gel alone.

Study SRE.2682

In Study SRE.2682 the photosensitization potential of a combination product with adapalene 0.1% and benzoyl peroxide gel 2.5% was tested in 33 healthy male or female subjects, 18 to 65 years old and meeting specific inclusion/exclusion criteria and compared to adapalene 0.1% gel alone, benzoyl peroxide 2.5% gel alone and the vehicle.

This study was to be conducted as a single-center, vehicle-controlled, single-blind (investigator/evaluator masked), intra-individual comparison with randomized applications. The MED (Minimal Erythema Dose) was to be determined for each subject at the Day 1 and Day 2 visits using full spectrum UV light.

The study then would consist of the 3 following phases:

Induction phase

One set of test products was to be applied under occlusive conditions on the upper back for 24 hours, twice weekly (e.g. Monday and Thursday) for 3 weeks (one additional site remained untreated). Twenty-four hours after product application the subjects had to return to the investigational center for product removal and irradiation (e.g. Tuesday and Friday). The irradiation dose was to be twice the subject's MED during the first week, and three times the subject's MED the second and the third week, using a total spectrum of UV light. According to the study visits schedule, skin reactions were to be assessed before application of test products and before irradiation of the sites.

Rest phase

2 weeks without product application/irradiation.

Challenge phase

Two sets of the 4 products were to be applied for 24 hours under occlusive conditions on naive sites on the lower back. Two untreated occluded sites were to be used as well. Each product was to be symmetrically located on each side of the back. Only the set located on the left side was to be irradiated with 0.5 MED full spectrum UV light followed by 4 J/cm2 UVA light. The non-irradiated sites were to serve as control for a possible contact sensitization. Skin reactions (erythema score + other local reactions) were to be scored before irradiation (60 minutes after product removal), and then 48 and 72 hours after end of irradiation.

Erythema was to be graded on a 5-point scale

0 No reaction
0.5 Erythema barely visible
1 Mild erythema
2 Moderate erythema
3 Severe erythema

At the end of the challenge phase, the Investigator was to assess the occurrence of a possible photoallergic reaction.

Diagnostic scale:

0 Negative
1 Equivocal
2 Positive photosensitization

In the event a subject would present a severe irritation reaction on any site (erythema rated 3 and/or if oozing, crusting and/or superficial erosion were noted), a change of patch site had to be considered. In the event the Subject developed a skin reaction of such nature or severity that it could be judged to be possibly a case of contact allergy, additional allergic tests could be conducted to determine the origin of the reaction. For example, the Subject could be patch tested with the study products supplied by the Sponsor at the Investigator's request.

According to the sponsor during this study, no clear-cut photosensitization reaction was observed. One equivocal reaction led to a further investigation which did not confirm photosensitization and was concluded to be irritant dermatitis.

7.4.6 Immunogenicity

This section is not applicable. The product is not a therapeutic protein.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

The only study appropriate for evaluating dose-dependency for adverse events is study SRE.2674 a right /left face comparison of adapalene 0.1% gel combined with either 2.5% or 5 % BP and then compared with 2.5%, 5% and 10% BPO alone.

Sixty subjects were randomized in four parallel groups and received the products as follows :

Group	*Number of subjects*	*Product application on one half-face*	*Product application on one half-face*
1	*15*	*Combination with 2.5% BPO*	*BPO 2.5%*
2	*16*	*Combination with 2.5% BPO*	*BPO 5%*
3	*15*	*Combination with 5% BPO*	*BPO 5%*
4	*14*	*Combination with 5% BPO*	*BPO 10%*

From the clinical study report No: RD.03.SRE.2674, page 3

The results of this study (which are summarized below) revealed that adverse events related to the product were significantly more common with the combination products and that the combination with 2.5%BPO was less irritating than the combination with 5%BPO.

Adverse Events (half faces) :	Combination with 2.5% BPO	Combination with 5% BPO	BPO 2.5%	BPO 5%	BPO 10%
n= (half-face)	31	29	15	31	14
Cutaneous related AEs* *(One AE was related to more than one product)	5	5	0	1	1
AE leading to discontinuation	2	4	0	1	0

Conclusion:

Analysis of the primary safety variable, (Total Sum Score (TSS)), demonstrated that the combination product with 5% BPO was statistically significantly more irritating than either BPO 5% or 10% alone. The combination product with 2.5% BPO was not statistically different from BPO 2.5% or 5%.

Analysis of the secondary safety variable, based on Worst Score of each individual signs/symptoms, confirmed these results.

Final version dated: 06 December 2002 PAGE 7
Clinical Study Report RD.03.SRE.2674, 5.3.5.4.1 pg.7

7.5.2 Time Dependency for Adverse Events

In the long term safety study 18089 most of the related AEs occurred within the first quarter (28.1%, 4.0%, 3.0%, and 1.5% in the first, second, third, and fourth quarters, respectively). A total of 110 subjects (24.3%) reported related dermatological AEs during the study and of those 94 subjects (20.8%) reported dermatological related AEs during the first quarter. For the most common adverse events in the combined pivotal studies the incidence "worse than baseline" were highest at week one and subsided thereafter as seen in figures 1-4 from the Summary of Clinical Safety (pg. 36-39).

Figure 1 Time course of Erythema, SRE.18094 and SRE.18087 Combined

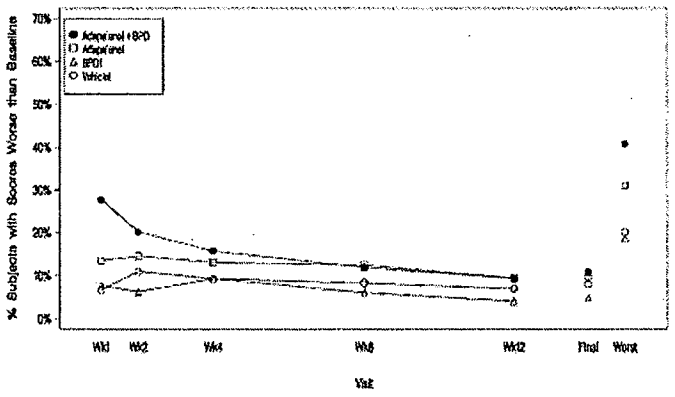

Figure 2 Time course of Scaling, SRE.18094 and SRE.18087 Combined

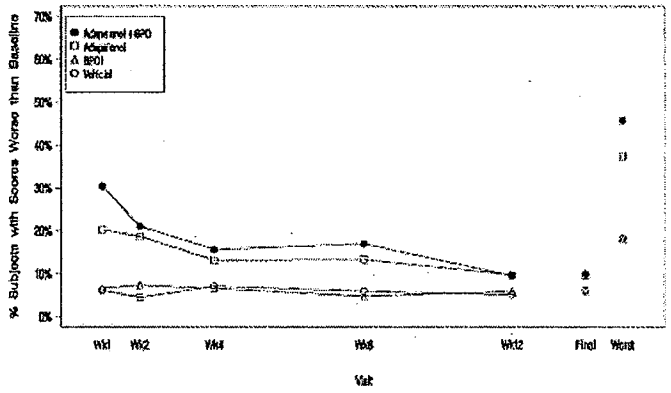

Figure 3 Time course of Dryness, SRE.18094 and SRE.18087 Combined

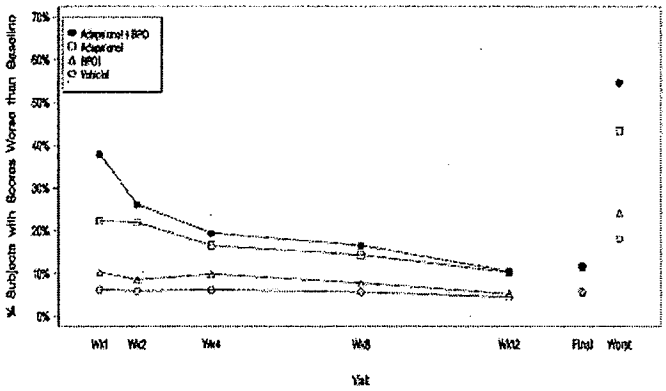

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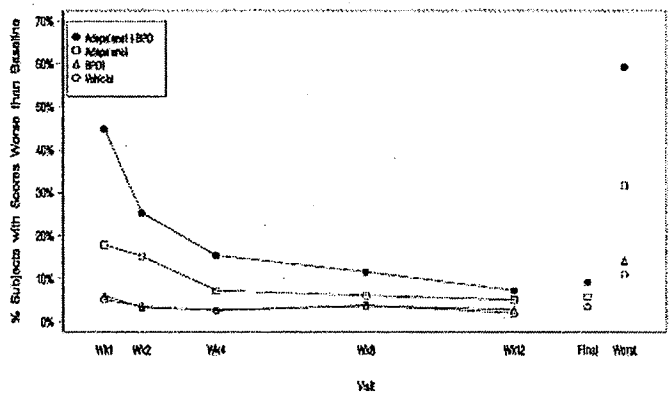
Figure 4 Time course of Stinging/Burning, SRE.18094 and SRE.18087 Combined



7.5.3 Drug-Demographic Interactions

In the combined pivotal studies 18087 and 18094 and in the long term safety study 18089 subgroup analyses of local tolerability and adverse events by gender (male and female), race (Caucasian and non-Caucasian), and age group (11 to 17 years and 18 to 64 years) are presented (see ISS pg. 60-62).

Table 24 Highest Severity of Local Tolerability Scores by Gender, SRE.18094 and SRE.18087 Combined, Number of Subjects and Percent Incidence

	Adapalene/Benzoyl Peroxide			Adapalene			Benzoyl Peroxide			Vehicle		
Subgroup	All	Male	Female	All	Male	Female	All	Male	Female	All	Male	Female
N[a]	553	291	262	562	287	275	557	300	257	481	235	246
Erythema[b] %	40.7	41.6	39.7	31.0	30.0	32.0	18.7	18.0	19.5	20.2	17.4	22.8
Scaling[b] %	45.8	40.5	51.5	37.5	33.4	41.8	18.0	15.7	20.6	18.3	15.3	21.1
Dryness[b] %	54.6	48.8	61.1	43.4	41.1	45.8	24.2	19.0	30.4	18.1	18.3	17.9
Stinging/Burning[b]	59.3	52.6	66.8	31.7	27.5	36.0	14.2	11.7	17.1	11.0	9.4	12.6

[a]: Total number of subjects with data available at baseline and post-baseline
[b]: Proportion of subjects with highest score worse than Baseline
Data Source: ISS Appendix 1, Tables 9.1, 9.2, 9.3, 9.4, 10.1.1, 10.1.2, 10.2.1, 10.2.2, 10.3.1, 10.3.2, 10.4.1, 10.4.2

With the exception of erythema in the combination group, the percentage of women experiencing issues of tolerability were higher than men across the groups and across the studies.

Table 25 Highest Severity of Local Tolerability Scores by Gender, SRE.18089, Number of Subjects and Percent Incidence

	Adapalene/Benzoyl Peroxide Gel		
Subgroup	All	Male	Female
N[a]	448	222	226
Erythema[b] %	48.0	51.4	44.7
Scaling[b] %	61.8	61.7	61.9
Dryness[b] %	65.2	62.6	67.7
Stinging/Burning[b] %	66.1	65.8	66.4

[a]: Total number of subjects with data available at baseline and post-baseline
[b]: Proportion of subjects with highest score worse than Baseline
Source: ISS Appendix 1, Tables 9.1, 9.2, 9.3, 9.4, 10.1.1, 10.1.2, 10.2.1, 10.2.2, 10.3.1, 10.3.2, 10.4.1, 10.4.2

From the sponsor's ISS, Appendix 1.

Findings for each subpopulation (gender, race, and age) were consistent with that observed for the total population.

Table 26 **Highest Severity of Local Tolerability Scores by Race, SRE.18094 and SRE.18087 Combined, Number of Subjects and Percent Incidence**

	Adapalene/ Benzoyl Peroxide			Adapalene Gel			Benzoyl Peroxide Gel			Gel Vehicle		
Subgroup	All	Cauc.	Non-Cauc.	All	Cauc.	Non-Cauc.	All	Cauc.	Non-Cauc.	All	Cauc.	Non-Cauc.
N[a]	553	367	186	562	381	181	557	367	190	481	316	165
Erythema[b] %	40.7	45.5	31.2	31.0	34.9	22.7	18.7	21.3	13.7	20.2	23.4	13.9
Scaling[b] %	45.8	51.0	35.5	37.5	40.9	30.4	18.0	20.7	12.6	18.3	22.2	10.9
Dryness[b] %	54.6	59.4	45.2	43.4	46.5	37.0	24.2	25.3	22.1	18.1	19.6	15.2
Stinging/Burning[b]%	59.3	59.4	59.1	31.7	29.9	35.4	14.2	12.3	17.9	11.0	9.2	14.5

[a]: Total number of subjects with data available at baseline and post-baseline
[b]: Proportion of subjects with highest score worse than Baseline
Data Source: ISS Appendix 1, Tables 9.1, 9.2, 9.3, 9.4, 12.1.1, 12.1.2, 12.2.1, 12.2.2, 12.3.1, 12.3.2, 12.4.1, 12.4.2

From the sponsor's ISS, Appendix 1.

Erythema, scaling and dryness were consistently more common in caucasians while stinging and burning were more common in non-caucasians with the exception of the combination group where they were essentially equal.

Table 27 **Highest Severity of Local Tolerability Scores by Race, SRE.18089, Number of Subjects and Percent Incidence**

Adapalene/Benzoyl Peroxide Gel			
Subgroup	All	Caucasian	Non Caucasian
N[a]	448	343	105
Erythema[b] %	48.0	52.5	33.3
Scaling[b] %	61.8	64.7	52.4
Dryness[b] %	65.2	66.5	61.0
Stinging/Burning[b] %	66.1	66.2	65.7

[a]: Total number of subjects with data available at baseline and post-baseline
[b]: Proportion of subjects with highest score worse than Baseline
Data Source: ISS Appendix 1, Tables 9.1, 9.2, 9.3, 9.4, 12.1.1, 12.1.2, 12.2.1, 12.2.2, 12.3.1, 12.3.2, 12.4.1, 12.4.2

From the sponsor's ISS, Appendix 1.

Table 28 **Highest Severity of Local Tolerability Scores by Age Group, SRE.18094 and SRE.18087 Combined, Number of Subjects and Percent Incidence**

	Adapalene/Benzoyl Peroxide			Adapalene Gel			Benzoyl Peroxide Gel			Gel Vehicle		
Subgroup	All	12-17	18-64	All	12-17	18-64	All	12-17	18-64	All	12-17	18-64
N[a]	553	382	171	562	390	172	557	388	169	481	319	162
Erythema[b] %	40.7	40.3	41.5	31.0	29.2	34.9	18.7	16.0	24.9	20.2	21.3	17.9
Scaling[b] %	45.8	44.8	48.0	37.5	36.7	39.5	18.0	17.3	19.5	18.3	20.7	13.6
Dryness[b] %	54.6	56.0	51.5	43.4	41.5	47.7	24.2	22.2	29.0	18.1	20.7	13.0
Stinging/Burning[b] %	59.3	60.2	57.3	31.7	27.7	40.7	14.2	13.1	16.6	11.0	9.1	14.8

[a]: Total number of subjects with data available at baseline and post-baseline
[b]: Proportion of subjects with highest score worse than Baseline
Data Source: ISS Appendix 1, Tables 9.1, 9.2, 9.3, 9.4, 11.1.1, 11.1.2, 11.2.1, 11.2.2, 11.3.1, 11.3.2, 11.4.1, 11.4.2

From the sponsor's ISS, Appendix 1.

There was no obvious discernible pattern in looking at tolerability based on age.

Table 29 **Highest Severity of Local Tolerability Scores by Age Group, SRE.18089, Number of Subjects and Percent Incidence**

	Adapalene/Benzoyl Peroxide Gel		
Subgroup	All	12-17	18-64
N[a]	488	298	150
Erythema[b] %	48.0	49.0	46.0
Scaling[b] %	61.8	64.4	56.7
Dryness[b] %	65.2	64.8	66.0
Stinging/Burning[b] %	66.1	68.5	61.3

[a]: Total number of subjects with data available at baseline and post-baseline
[b]: Proportion of subjects with highest score worse than Baseline
Data Source: ISS Appendix 1, Tables 9.1, 9.2, 9.3, 9.4, 11.1.1, 11.1.2, 11.2.1, 11.2.2, 11.3.1, 11.3.2, 11.4.1, 11.4.2

From the sponsor's ISS, Appendix 1.

7.5.4 Drug-Disease Interactions

The efficacy data collected allowed for capture of disease exacerbation during treatment but failed to reveal any significant findings.

7.5.5 Drug-Drug Interactions

No specific studies of potential drug interactions were performed during the development program for Adapalene/Benzoyl Peroxide Gel. Such studies were not considered necessary, given the cutaneous topical route of administration, the limited systemic availability of adapalene, the rapid and complete conversion of benzoyl peroxide to benzoic acid, and the post-marketing experience available with other adapalene topical dosage forms and concentrations.

From previous experience with adapalene and benzoyl peroxide, there are no known interactions with other medicinal products which might be used topically and concurrently with Adapalene/Benzoyl Peroxide Gel. Interaction with systemic medicinal products is unlikely since the absorption of Adapalene from the fixed combination through human skin is low. The percutaneous penetration of benzoyl peroxide in the skin is also low and what is absorbed is completely converted into benzoic acid which is rapidly eliminated. Therefore, the potential interaction of benzoic acid with systemic medicinal products is also unlikely to occur.

7.5.6 Additional Safety Explorations

There were no additional safety explorations.

7.5.7 Human Carcinogenicity

Information on nonclinical carcinogenicity studies with adapalene from the Adapalene 0.3% label approved on 6/19/07 are as follows:

> Carcinogenicity studies with adapalene have been conducted in mice at topical doses of 0.4, 1.3, and 4.0 mg/kg/day, and in rats at oral doses of 0.15, 0.5, and 1.5 mg/kg/day. These doses are up to 3 times (mice) and 2 times (rats) in terms of mg/m^2/day the potential exposure at the maximum recommended human dose (MRHD), assumed to be 2.5 grams DIFFERIN Gel, 0.3%. In the oral study, increased incidence of benign and malignant pheochromocytomas in the adrenal medullas of male rats was observed.
>
> No photocarcinogenicity studies were conducted. Animal studies have shown an increased risk of skin neoplasms with the use of pharmacologically similar drugs (e.g., retinoids) when exposed to UV irradiation in the laboratory or to sunlight. Although the significance of these studies to human use is not clear, patients should be advised to avoid or minimize exposure to either sunlight or artificial UV irradiation sources.
>
> Adapalene did not exhibit mutagenic or genotoxic effects in vitro (Ames test, Chinese hamster ovary cell assay, mouse lymphoma TK assay) and in vivo (mouse micronucleus test).

Information on nonclinical carcinogenicity studies with benzoyl peroxide from the Duac label approved on 11/17/03 are as follows:

Benzoyl peroxide has been shown to be a tumor promoter and progression agent in a number of animal studies. The clinical significance of this is unknown.

Benzoyl peroxide in acetone at doses of 5 and 10 mg administered twice per week induced squamous cell skin tumors in transgenic TgAC mice in a study using 20 weeks of topical treatment.

Genotoxicity studies were not conducted with Duac Topical Gel. Benzoyl peroxide has been found to cause DNA strand breaks in a variety of mammalian cell types, to be mutagenic in Salmonella typhimurium tests by some but not all investigators, and to cause sister chromatid exchanges in Chinese hamster ovary cells.

7.5.8 Human Reproduction and Pregnancy Data

No specific studies in pregnancy and lactation were performed with Adapalene/Benzoyl Peroxide Gel. Information on reproductive function and fertility studies with adapalene from the Adapalene 0.3% label approved on 6/19/07 are as follows:

> Reproductive function and fertility studies were conducted in rats administered oral doses of adapalene in amounts up to 20 mg/kg/day (up to 26 times the MRHD based on mg/m^2 comparisons). No effects of adapalene were found on the reproductive performance or fertility of the F0 males or females. There were also no detectable effects on the growth, development and subsequent reproductive function of the F1offspring.

Up to the cut-off date of September 28, 2007, a total of 13 pregnancies were reported (six (6), one (1), one (1) and five (5) in the Adapalene/Benzoyl Peroxide Gel, Adapalene Gel, Benzoyl Peroxide Gel, and Gel Vehicle groups, respectively) in the completed clinical development program. In the Adapalene/BPO Gel group 3 pregnancies reported normal outcomes and 3 are continuing.

A total of seven pregnancies were reported in studies SPR.18088 and SPR.29058 both of which are ongoing, five (5) are continuing to show a normal progression and no abnormalities. One subject underwent an elective abortion and one subject was lost to follow up.

There have been six cases of pregnancies reported in clinical studies conducted with Adapalene 0.3% gel and one case was reported in a patient following exposure to different formulations of adapalene cream (0.05%, 0.2%, 0.3%). Of those 7 pregnancies, four subjects delivered healthy babies, 2 subjects underwent elective abortion (1 was exposed to Adapalene 0.3% and 1 was exposed to a different formulation of adapalene cream (0.05%, 0.2%, 0.3%)). One subject was lost to follow-up, thus, the outcome of the pregnancy is unknown.

In the small sample of adapalene-exposed pregnancies, the rates of congenital malformation and

spontaneous abortion are not statistically different from expected rates reported in the literature.

Since the launch of Differin (adapalene) 0.1% gel up to the safety-reporting cut-off date for this NDA of September 28, 2007, 168 cases of pregnancies have been reported, including the cases reported during clinical trials. Of those 168 cases, 95 pregnancies with a known outcome could be analyzed. Among these 95 pregnancies, 67 (70.8%) presented with a normal outcome, 6 (6.3%) with a congenital malformation or functional anomaly, 11 (11.5%) presented with a spontaneous abortion, 8 (8.4%) with an elective abortion, one case of an ectopic pregnancy, one case of premature baby's death, and one case of premature separation of the placenta which led to fetal death were also reported.

Benzoyl peroxide, at concentrations up to 20% w/w, has been in widespread clinical use for the cutaneous treatment of acne vulgaris for several decades. Sixteen (16) cases of pregnancies were reported, including one case reported during a clinical trial. Among these 16 pregnancies, five subjects delivered healthy babies, two subjects reported babies with a congenital anomaly (one case with a cleft lip and interventricular septal defect, and one case with a ectopic testes and a teratoma diagnosed at the age of 2 months). Eight of 16 subjects were lost to follow-up, and one case is still on-going.

7.5.9 Pediatrics and Effect on Growth

No assessment has been made on the effects of Adapalene/Benzoyl Peroxide Gel on growth.

7.5.10 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Overdose

Adapalene/Benzoyl Peroxide Gel is for once-daily cutaneous use only. In case of accidental ingestion, appropriate symptomatic measures should be taken.

Drug Abuse

No investigations of the dependence potential of Adapalene/Benzoyl Peroxide Gel were performed. Such studies were not considered to be warranted given the cutaneous route of administration, the limited systemic availability of both adapalene and benzyol peroxide following cutaneous administration, and the extensive post marketing experience with other adapalene and benzoyl peroxide products.

Withdrawal and Rebound

No investigations were performed to evaluate the potential for withdrawal and rebound effects following use of Adapalene/Benzoyl Peroxide Gel. Nevertheless, in the Well Controlled

Efficacy and Safety Studies (SRE.18094 and SRE.18087) and the Long Term Safety and Efficacy Study (one year) SRE.18089, no withdrawal or rebound effects were reported for subjects with cleared acne who stopped their study medication but continued in the study.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

Adapalene/Benzoyl Peroxide Gel has limited systemic availability and effects on ability to drive, ability to operate machinery, or mental ability are unlikely to occur.

7.6 Additional Submissions

A 4-Month Safety Update was received on June 6, 2008. Review did not reveal new information that would affect labeling.

8 Postmarketing Experience

The sponsor asserts that adapalene/benzoyl peroxide gel is not marketed outside of the United States. Adapalene and benzoyl peroxide have been marketed individually for acne vulgaris in various formulations and various concentrations for years.

9 Appendices

9.1 Literature Review/References

The sponsor submitted the application under Section 505(b)(2) of the Act. Per Section, 3.6.2, the application relied on nonclinical pharmacology and toxicology data available from the literature for adapalene and benzoyl peroxide. The sponsor also submitted clinical references that discussed the individual moieties.

9.2 Labeling Recommendations

Labeling review is ongoing at the time of this review. Final labeling will be appended to the action letter, if approved. Below is the sponsor's proposed labeling with this reviewer's initial revisions.

11 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Medical- 1

10.1 Advisory Committee Meeting

No advisory committee meeting was held for this product.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jane Liedtka
10/23/2008 02:09:22 PM
MEDICAL OFFICER

Jill Lindstrom
10/28/2008 05:54:13 PM
MEDICAL OFFICER

DDDP CLINICAL FILING CHECKLIST FOR A NEW NDA/BLA

	Yes	No	N/A	Comment
FORMAT/ORGANIZATION/LEGIBILITY				
1. Identify the general format that has been used for this application, e.g. electronic CTD.	eCTD			
2. On its face, is the clinical section of the application organized in a manner to allow substantive review to begin?	X			
3. Is the clinical section of the application indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4. For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5. Are all documents submitted in English, or are English translations provided when necessary?	X			
6. On its face, is the clinical section of the application legible so that substantive review can begin?	X			
LABELING				
7. Has the applicant submitted draft labeling in electronic format consistent with 21 CFR 201.56[1] and 201.57, current divisional and Center policies, and the design of the development package?	X			
SUMMARIES				
8. Has the applicant submitted all the required discipline summaries (*i.e*, Module 2 summaries)?	X			
9. Has the applicant submitted the integrated summary of safety (ISS)?	X			M5.3.5.3
10. Has the applicant submitted the integrated summary of efficacy (ISE)?	X			M5.3.5.3
11. Has the applicant submitted a benefit-risk analysis for the product?	X			M2.5.6.2
12. Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	505(b)(2) published literature			
DOSE				
13. If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: SRE.2674 Study Title: INTRA-INDIVIDUAL EVALUATION OF CUTANEOUS TOLERANCE OF A ONCE DAILY COMBINATION ADAPALENE 0.1% AND BENZOYL PEROXIDE 2.5% OR 5% GEL BENZOYL PEROXIDE 2.5%, 5% OR 10% GEL IN HEALTHY VOLUNTEERS Sample Size: 60 Arms:4 Arms Location in submission: M 2.5.3.1	X			
EFFICACY				
14. On its face, do there appear to be the requisite number of adequate and well controlled studies in the application? Pivotal Study #1 18094 Indication: Acne Vulgaris M5.3.5.1 Pivotal Study #2 18087 Indication: Acne Vulgaris	X			

[1] http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr201_01.html

15. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16. Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17. Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		X		IR
SAFETY				
18. Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19. Has the applicant submitted adequate information to assess the arrythmogenic potential of the product (*e.g.*, QT interval studies, if needed?		X		IR
20. Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product?			X	Available for monads
OTHER STUDIES				
21. Has the applicant submitted all special studies/data requested by the Division during the pre-submission discussions with the sponsor?				
22. For an Rx-to-OTC switch application, are the necessary special OTC studies included (*e.g.*, labeling comprehension)?			X	
PEDIATRIC USE				
23. Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			No substantiation
ABUSE LIABILITY				
24. If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES				
25. Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X		IR
DATASETS				
26. Has the applicant submitted datasets in a format to allow reasonable review of the patient data?		X		See appended stats response
27. Has the applicant submitted datasets in the the format agreed to previously by the Division?			X	
28. Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			See appended stats response
29. Are all datasets to support the critical safety analyses available and complete?	X			

30. For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints?	X			
CASE REPORT FORMS				
31. Has the applicant submitted all required Case Report forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			5.3.1.24
32. Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE				
33. Has the applicant submitted the required Financial Disclosure information for study investigators?	X			1.3.4
GOOD CLINICAL PRACTICE				
34. Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?		X		IR
CONCLUSION				
35. From a clinical perspective, is this application fileable? If "no", please state why it is not?				

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

A)Filing review issue:

Insufficient information has been provided to assess the effect of the product on cardiac repolarization.

B)The following information request should be included in the 74 day letter.

The sponsor is asked to provide the following:

a) information to assess the effect of the product on cardiac repolarization
b) a rationale for assuming the applicability of foreign data in the submission to the US population
c) substantiation for a pediatric waiver for age 12 and under
d) with regard to datasets, the sponsor's method of recording visit make it difficult to track subject response across time, especially when no date of visit is recorded, please correct this to allow tracking
e) though datasets are complete they cannot be merged by subject ID and visit, please correct to allow merge
f) a statement of Good Clinical Practice for all of the clinical studies

Jane Liedtka, M.D.
3/20/08

Reviewing Medical Officer

Clinical Team Leader

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jane Liedtka
5/2/2008 10:29:23 AM
MEDICAL OFFICER